Catalytic Hydrogenation over Platinum Metals

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Preface

Catalytic hydrogenation is a powerful means of achieving controlled transformations of organic compounds. This work is concerned with the kinds of transformations that can occur and how they can be achieved over platinum metal catalysts. The latter are the most widely used of all hydrogenation catalysts, and much of what can be accomplished with hydrogenation can be done best over platinum metals. The work is organized according to the chemistry of hydrogenation of individual functional groups with further subdivision dictated by available data. Particular emphasis is given to the manner in which hydrogenation may be altered by the catalytic metal, catalyst support, reaction environment, and catalyst modifiers. There is very little discussion of the mechanisms of catalysis: practical problems in catalysis are solved most easily by an empirical approach coupled with a thorough knowledge of the literature.

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Platinum Metal Catalysts

I. PLATINUM METALS

The six elements in the platinum metals group (Table I) are all hydro-genation catalysts. Palladium and platinum catalysts have been widely used for decades. Rhodium and ruthenium also make excellent hydrogenation catalysts, but their merits are not yet so widely appreciated (most references to these catalysts date from the middle fifties). Iridium and osmium have found still less use. Osmium hydrogenation catalysts do not appear to have exceptional merit; whether this is due to some intrinsic property of osmium or to inadequate procedures in the catalyst preparation is not yet known. Iridium, on the other hand, makes a fair catalyst and its lack of use stems partly from neglect and partly from the fact that some platinum metal has usually proved more suitable whenever a comparison was made.

The platinum metals make exceptionally active hydrogenation catalysts, and most functional groups can be reduced under mild conditions over one or another of these catalysts. Many industrial hydrogenation processes are carried out at elevated pressure and/or temperature, however, to make more

TABLE I

PLATINUM METALS[a]

Element	Symbol	Atomic number	Atomic weight
Ruthenium	Ru	44	101.07
Rhodium	Rh	45	102.905
Palladium	Pd	46	106.4
Osmium	Os	76	190.2
Iridium	Ir	77	192.2
Platinum	Pt	78	195.09

[a] A review of the physical properties of the platinum metals and gold and silver has been published in *Engelhard Ind. Tech. Bull.* **6**, 61 (1965).

efficient use of the metal and hydrogenation equipment. The most effective metal varies with each substrate, but enough data have accumulated to permit a satisfactory selection of catalyst and conditions for successful reduction of most substrates without undue difficulty.

II. TYPES OF CATALYST

Platinum metal hydrogenation catalysts are of two types—supported and unsupported, with the latter group being further divided into those for use in slurry processes and those for use in fixed-bed operation. In batch-type hydrogenations the support is usually a fine powder. Occasionally a coarser support is used, so that on completion of the reaction the catalyst settles and can be recovered by decantation rather than filtration. Catalyst supports for use in fixed-bed operation are usually in the form of cylinders, spheres, or granules with particle size of roughly $\frac{1}{4} - \frac{1}{32}$ inches.

A. UNSUPPORTED CATALYSTS

Early in the century, platinum metal catalysts were usually in the form of finely divided metal or metal oxide (Sabatier, 1923). The metals are referred to as blacks, and, if stabilized in solution by substances such as gum arabic (Skita, 1912) or polyvinyl alcohol (Rampino and Nord, 1941), as colloidal catalysts. Platinum metal oxides and blacks are still widely used and may be preferred to supported catalysts with compounds difficult to hydrogenate, or when substantial yield losses occur through absorption of products by the catalyst support (Barnes and Fales, 1953), or when overly strong adsorption on the support poisons the catalyst. Unsupported metal is used less efficiently than supported metal and recovery losses are likely to be higher.

B. SUPPORTED CATALYSTS

Supported platinum metal catalysts have a number of advantages over unsupported catalysts. The support permits greater efficiency in use of the metal by increasing the active metal surface and by facilitating metal recovery. Also, supported catalysts have a greater resistance to poisoning. Perhaps the greatest value of a support is that it provides a further control over selectivity.

Platinum metals have been supported on a variety of materials, including such diverse substances as carbon, alumina, silica, alkaline earth carbonates and sulfates, zinc, asbestos, and silk. The list could be extended greatly. One gathers that almost any material of suitable form and stability can be used

as a catalyst support. The relationship between performance and support is extremely complex for, among other things, performance is related to the particular sample of support examined (Maxted and Elkins, 1961), to the precise method of metal deposition, and to the system in which the catalyst is used. Among the physical properties of a support that may influence performance are total surface area, average pore size, pore size distribution, and particle size, insofar as these properties affect the metal dispersion and control the transport of reactants and products to and from the catalyst surface.

Relatively little effort has been made in liquid phase catalysis to disentangle the multiple contributions, both chemical and physical, of a support to catalyst performance, but in special instances particular characteristics have been singled out. For instance, the activity differences found in platinum-on-alumina, platinum-on-zirconia, and platinum-on-chromium sesquioxide, when used for hydrogenation of cyclohexene and ethyl crotonate, have been related to mean pore radius of these supports; correlations between activity and surface area of the platinum metal (Maxted and Elkins, 1961), or in supported palladium catalysts between activity and surface area of the support, were not evident (Maxted and Ali, 1961). On the other hand, the marked difference in isomer distribution obtained on hydrogenation of hexahydroxybenzene over colloidal palladium and over 10% palladium-on-carbon was attributed to the greater surface area of the latter (Angyal and McHugh, 1957). The products of hydrogenation may also change with the support, inasmuch as various supports, for whatever reason, give catalysts of differing activities and consequently different levels of hydrogen availability at the catalyst surface (Zajcew, 1960; Augustine, 1963). Supports, or the catalyst as a whole, may also influence the product insofar as they contain trace quantities of free acid or alkali.

1. Agglomeration

Supports may affect catalyst activity, as the support partly determines the tendency of a catalyst to agglomerate or to stick to the reactor walls. The factors determining the degree of agglomeration are indeed subtle, for the extent of agglomeration may change markedly with the support, the reaction, and minor changes in the reaction system. Catalyst clumping is a common cause of unsatisfactory results. This difficulty can usually be overcome by a change of support, amount of catalyst, agitation, solvent, or even reactor size.

2. Resistance to Poisoning

Metals on different supports vary in resistance to poisoning by extraneous contaminants and by products of the reduction. The effect that a product

of reduction may have on the catalyst is illustrated by hydrogenation of nitrobenzene in cyclohexane solvent over 5% palladium-on-carbon and 5% palladium-on-alumina. Both catalysts had the same initial rate, and over the carbon-supported catalyst the reaction continued unabated almost until completion. However, over the alumina catalyst the rate declined sharply to one sixth of the original rate when the reaction was about 30% complete. When water, equal to the amount formed at this point, was added initially the reduction began at and maintained this lower rate. In this system, palladium-on-calcium carbonate tended to stick to the walls of the reactor and was largely unavailable for use (Rylander et al., 1965). The support may also influence the course of reduction and the amount of various inhibiting by-products.

In general, supported catalysts show a greater resistance to poisoning than nonsupported catalysts, probably because the support increases the active surface (Germain et al., 1961). Also, the support itself may sop up catalyst poisons and inhibitors; the performance of unsupported catalysts can often be improved by adding a catalyst support, such as high surface carbon, to the reaction mixture.

3. Effect of Particle Size on Activity

The activity of a catalyst is related to the particle size of the support, as illustrated by the data of Table II (Rylander et al., 1965). A 1% platinum-on-carbon catalyst was divided by screening into five portions, and an equal weight of each portion was used in hydrogenation of nitrobenzene dissolved in acetic acid. Only part of the marked increase in rate with decreasing particle size can be attributed to the higher percentages of metal found on the smaller particles; most of the increase must be attributed to better transport of reactants to the catalysts. The rate advantages obtained by

TABLE II

EFFECT OF PARTICLE SIZE ON RATE OF HYDROGENATION[a]

(Hydrogenation of Nitrobenzene in Acetic Acid)

Particle size	Percent Pt on support	Relative rates based on equal weights of catalyst
40–60 mesh	1.0	1.0
60–80 mesh	1.0	1.6
80–100 mesh	1.02	1.9
100–150 mesh	1.07	2.5
through 150 mesh	1.43	5.9

[a] 100 mg platinum-on-carbon catalyst, room temperature, atmospheric pressure.

using very fine particles are in practice offset by increasing catalyst cost and by difficulties in filtration. The best catalysts combine a sufficiently fast rate with easy recovery. Rampino and Nord (1941) have examined the complex relationship between particle size and rate of hydrogenation over palladium and platinum-polyvinyl alcohol colloidal catalysts.*

4. Economical Use of Metal

In general, supported catalysts provide much more economical use of the metal. For example, hydrogenation of heptaldehyde over equal weights (on a metal basis) of 5% platinum-on-carbon and over platinum oxide proceeded about eight times more rapidly over the former (Rylander and Kaplan, 1961). Similar comparisons are common. In addition, supported catalysts may be more easily filtered, and mechanical losses of the metal will be proportionately less when handling a metal diluted by a support.

5. Concentration of Metal

Platinum metal catalysts for use in batch processing usually contain about 1–10% by weight of metal, although special purpose catalysts containing as much as 30–40% by weight of metal are made and used commercially. Fixed-bed catalysts contain generally about one tenth as much metal as powdered catalysts. The percentage of metal on a catalyst has, with a number of exceptions, little effect on the product, and the question of appropriate metal concentrations is determined in most instances more by economic than technical considerations. More efficient use is made of the metal as the concentration of the metal is lowered (Table III) (Karpenko, 1964), but the

TABLE III

HYDROGENATION OF NITROBENZENE IN ACETIC ACID[a]

Catalyst	Catalyst (mg)	Pd (mg)	Relative rate
1% Pd-on-carbon	500	5	7.6
3% Pd-on-carbon	166	5	3.5
5% Pd-on-carbon	100	5	1.8
10% Pd-on-carbon	50	5	1.2
30% Pd-on-carbon	16.6	5	1.0

[a] Each experiment was carried out at room temperature and atmospheric pressure with 500 mg total carbon carrier present. Not all substrates show as large a variation in rate with percent metal as shown here; the magnitude of the change depends among other things on the substrate (Young and Hartung, 1953).

* Manufactured by Engelhard Industries, Newark, N.J.

increased efficiency is offset by increasing catalyst costs. Since the platinum metal is ordinarily reclaimed, the metal cost is not the major factor in the total cost of the catalyst. In the United States, 5% metal-on-powdered carrier catalysts are used widely, the economics being such that metal concentrations in this range will give the most product per dollar of total catalyst cost. When the metal is recovered, 10% metal-on-carrier catalysts are only slightly more expensive to use than 5%. In England, where labor costs are different, 3% catalysts are more popular.

6. *Asymmetric Supports*

Asymmetric syntheses may be achieved by catalytic hydrogenations carried out over a platinum metal deposited on an asymmetric surface, as *d*- or *l*-quartz or silk fibroin, but the optical purity is usually not high. Optically active phenylalanine was obtained in 25% optical purity by the hydrogenation of ethyl α-acetoximino-β-phenylpyruvate over palladium-on-silk fibroin at 70°C and 1350 psig pressure, followed by acid hydrolysis of the product. Optically active phenylalanine was also derived by hydrogenation of 4-benzylidene-2-methyloxazol-5-one under similar conditions over a palladium-on-silk catalyst (Akabori *et al.*, 1956, 1957). There is some evidence that catalyst sites may be asymmetric and present with an equal number of the mirror images. In support of this suggestion was the observation that an optically active compound was not reduced as fast as the racemic mixture (Beamer *et al.*, 1960).

7. *Choice of Support*

The rate and, at times, the products of reduction vary with the catalyst support. The literature records many examples (Rylander *et al.*, 1965) where one catalyst support was preferred to another, but guiding principles for choice have yet to be developed. An understanding of the influence of carrier on the rate and course of reduction from preferences recorded in the literature is particularly difficult to achieve, because one is never certain whether it was the support itself, the method of catalyst preparation, or some unknown factor that was responsible for the differential results. Even in controlled studies it is difficult to disentangle effects produced by the support itself from various other factors involved in the comparison. For instance, optimum catalysts are not produced if all catalysts are prepared by the same technique regardless of support, but if the technique is altered an additional variable will be introduced.

In practice it is usually not difficult to pick a satisfactory support. Unless there is evidence to the contrary, either carbon or alumina is an excellent first choice and either will prove adequate for most reductions. Beyond this

broad generality the best guide is a suitable precedent; examples of satis-
factory results with other carriers are given throughout this text. Alkaline
earth carbonate or sulfate supports seem to give quite often better selectivity
than carbon- or alumina-supported catalysts. For instance, hydrogenation
of *trans*-dibenzoylethylene over palladium-on-carbon afforded dibenzoyl-
ethane in 58% yield and 1,2,3,4-tetrabenzoylbutane in 36% yield; over
palladium-on-strontium carbonate the product was 97% dibenzoylethane
(McQuillin *et al.*, 1963).

III. SYNERGISM

Two platinum metal catalysts when used together may sometimes give
better rates or better yields than either catalyst individually. Synergistic
effects have been observed when two separate catalysts were mixed together
mechanically, and also when two metals were incorporated in a single
catalyst. Synergism by mixtures of two catalysts has been accounted for by
the assumption that hydrogenation involves two or more discrete stages, or
multiple intermediates, some of which may be reduced more easily by one
catalyst and some by the other (Rylander and Cohn, 1961). Synergism in
coprecipitated or co-fused mixed metal catalysts may be accounted for
similarly, as well as by formation of alloys, by alterations in electronic
constitution, and by changes in particle size and surface area.

A. Mixtures of Catalysts

Two platinum metal catalysts used simultaneously may give better results
than the catalysts used individually or consecutively (Baer *et al.*, 1952).
Overberger and Lapkin (1955) were able to reduce a complex cyclic azine
only over a mixture of platinum oxide and 10% palladium-on-carbon.
Reductions over the individual catalysts were unsuccessful. A mixture of
5% platinum-on-carbon and 5% palladium-on-carbon gave better yields
of 2-amino-1-phenyl-1-propanol by hydrogenation of isonitrosopropio-
phenone than were obtained with either catalyst individually (Wilbert and
Sosis, 1962). This particular reduction is sensitive to only a few percent of
platinum or rhodium incorporated in the palladium catalyst (Hartung and
Chang, 1952). Synergism occurred also in hydrogenation of nitro compounds,
nitriles, and acetylenes over mixtures of palladium or platinum catalysts
and ruthenium catalysts (Rylander and Cohn, 1961). In these reductions,
ruthenium alone was completely inactive.

Except for certain selected examples, there seems to be no way of predicting
when mixtures of catalysts will prove advantageous. Their use complicates

recovery and extends the already large number of reasonable choices. Nonetheless, a mixture may well be worth resorting to when individual catalysts have proved unsatisfactory. A number of workers have used mixtures for no clearly stated reason (Gutsche *et al.*, 1961; Butz *et al.*, 1947; Mariella and Havlik, 1952; Mariella and Belcher, 1951; Harris and Folkers, 1939; Wright, 1959).

B. MIXED-METAL CATALYSTS

Many catalysts with two platinum metals intermingled have been prepared and some show large synergistic effects. The metals may be colloidal mixtures, fused oxides, or co-supported. As with mixtures of catalysts, there seems to be no way of predicting in general when mixed-metal catalysts will prove effective. These catalysts often have special properties and are worthy of consideration when other catalysts have proved unsatisfactory. Inasmuch as the effectiveness of this type of catalyst varies markedly with both the metal ratio and the substrate, catalyst testing is tedious. A useful but not infallible guide to the probable effectiveness of coprecipitated metal catalysts is the performance of a mechanical mixture of the two metals. If synergism results from the mechanical mixture, it probably will also in a catalyst of coprecipitated metals. In this way various combinations of metals may be tested without actually preparing the mixed metal catalyst.

Impressive examples of synergism with colloidal palladium and platinum catalysts have been reported (Rideal, 1920). A series of catalysts, stabilized by gum arabic, was made with varying proportions of palladium and platinum. The addition of only a small amount of palladium to a platinum sol greatly enhanced its activity and extended the life. The suggestion was made that promoters may in part function as peptizing agent for colloidal catalysts, or for catalysts that pass through a colloidal stage at some point in their preparation.

Mixed rhodium–platinum oxides* prepared by fusion with sodium nitrate showed properties not found in either oxide separately. These mixed catalysts were especially recommended when hydrogenolysis was to be avoided (Nishimura, 1961a). Platinum–ruthenium oxides, prepared in similar manner, showed surprisingly high activities in certain reductions. The optimum ruthenium content depended in a striking way on the substrate; for pyridine and 2-methylbut-3-yn-2-ol it was 3 atom percent ruthenium, for cyclohexene, cyclohexanone, and acetophenone 30 atom percent ruthenium. Mechanical mixtures of platinum oxide and rhodium oxide did not function in the same way as the co-fused metals (Bond and Webster, 1964).

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* Many binary and ternary platinum metal catalysts have been prepared by this and other methods (O. J. Adlhart and J. G. E. Cohn, French Patent 1,407,903).

Platinum metals coprecipitated on a support (Koch, 1962, 1965; Rylander and Koch, 1965) may have unusual properties. Reduction of 1,2,3,4-tetrahydroacridine in methanol occurred readily over a palladium–platinum-on-carbon catalyst, but failed or was very slow over palladium-on-carbon, platinum-on-carbon, or Raney nickel (Hayashi and Nagao, 1964). Enhanced rates were observed in hydrogenation of butynediol over palladium–ruthenium-on-carbon catalysts and of nitrobenzene over platinum–ruthenium catalysts (Rylander and Cohn, 1961). Certain advantages have been claimed for ruthenium–palladium catalysts in hydrogenation of glucose to sorbitol (British Patent 867,689).

Even very small percentages of a second platinum metal may cause marked synergism. The reduction of quinone over palladium-on-carbon was more rapid when only 2 atoms per hundred (based on palladium) of rhodium, ruthenium, platinum, osmium, or iridium was incorporated in the catalyst. On the other hand, all these mixed metal catalysts were less active than pure palladium-on-carbon when the substrate was benzaldehyde. Reduction of piperonal oxime over palladium-on-carbon was promoted by ruthenium but strongly inhibited by platinum or iridium (Young and Hartung, 1953). The authors advanced some explanations for these results.

IV. CATALYST STABILITY

Most platinum metal catalysts can be kept apparently unchanged for years, provided they are stored in a container sealed against contaminants in the atmosphere. There are some exceptions. A number of workers have commented on the loss of activity of platinum oxide catalysts with aging, and the suggestion has been made that platinum oxide catalysts should preferably be made as needed, for in certain cases (unspecified) the catalyst decreases in activity after standing several weeks (Adams et al., 1946). A decline in activity of platinum oxide was observed during a study extending over only 2 months. The authors (Siegel and Dmuchovsky, 1964) commented that platinum oxide does not seem to be ideally suited for quantitative work. Smith and Burwell (1962) noted that if platinum oxide is evacuated for 4 days before use, during which time the catalyst changes color, the initial activity is about 1.6 times greater than usual. That platinum oxide sometimes changes activity with aging is certain, but under what circumstances has not been established; we and others have kept platinum oxide for years apparently unchanged.

Despite various reports that catalysts age, and some assuredly do, it is substantially correct to assume that most catalysts, for all practical purposes, do not age. We have kept a variety of catalysts in our laboratory for many years without any significant changes in activity. We have the impression

that the induction period characteristically shown by ruthenium catalysts increases with age of the catalyst, but the activity remains essentially constant. An accurate check on a change in activity after a lapse of considerable time is a formidable problem. Organic substrates are themselves subject to change over long periods of time and there is no guarantee that a new sample of substrate will be identical to an earlier material. A colloidal palladium stored for 15 years was found to be more active than a fresh preparation in hydrogenation of tetraphenylbutynediol but less active toward tetra-methylbutynediol (Sokol'skii, 1964a); one explanation for these results is that the substrates differed.

V. SAFETY

Platinum metal catalysts are generally nonpyrophoric and can be safely held in the hand. However, they catalyze the oxidation of organic com-pounds and great care must be taken when the catalysts are brought into contact with organic liquids or combustible vapors. Platinum metal catalysts, especially platinum or palladium, are prone to ignite lower alcohols. In our laboratory it is routine practice to cool both the dry catalyst and alcohol in ice or Dry Ice before mixing. Alternatively, the alcohol is added to the catalyst in a flask filled with nitrogen. Especially active catalysts are both cooled and blanketed with nitrogen. Once the catalyst has been wet with alcohol, the possibility of ignition is greatly diminished. It is therefore a mistake to try to prevent fires by adding the solvent dropwise; it is safer to drown the catalyst with liquid.

Platinum metal catalysts-on-carbon can be supplied commercially as 50% water-wet, free-flowing powders* and are recommended when using alcohol as a solvent. The chance of fire is greatly diminished when using these catalysts, but nonetheless safety precautions should not be relaxed. Water-wet powders also reduce the possibility of a dust explosion. Although dry, powdered carbon catalysts have been used for years without mishap, they present the same hazards as any other finely divided, combustible powder and adequate precautions should be taken.

Over many years we have never had fires in our laboratory when mixing catalysts with carboxylic acids, alcohol-free esters, ethers, or hydrocarbons as solvents, although no special precautions were taken. This statement is intended to imply only that materials of these types are not readily ignited by hydrogen-free catalysts; in no sense does it imply that they cannot be. After a catalyst has been used and is saturated with hydrogen, any com-bustible vapor might be ignited, inasmuch as the catalyst itself may catch

* Manufactured by Engelhard Industries, Newark, N.J.

fire when exposed to air. A used filtered catalyst should be wetted and kept out of contact with combustible vapors.

In large-scale processing, the hazards of damage and injury by fire are increased. Rebenstorf (1966) has recommended that procedures in large-scale hydrogenation be standardized and the sequence of operations reduced to a check-list. This scheme is particularly useful when the actual handling of catalysts and reaction materials is carried out by nontechnical personnel.

VI. CATALYST REUSE

In commercial operation a catalyst should be reused as many times as possible, for each reuse lowers the cost of the catalyst per pound of product. There is apparently no way of knowing in advance how many times a catalyst can be reused. The total catalyst life, with or without intervening regenerations, is best determined experimentally with the materials to be actually used in the reduction. Often there is some decline in activity with each reuse, and it is common practice to add a small amount of fresh catalyst occasionally so as to maintain a constant overall activity and reaction time for the batch (McElvain and Adams, 1923). Ruthenium catalysts typically do not reach maximum activity until the second or third use (Rylander et al., 1963). The amount of material that may be reduced through repeated reuse of a catalyst is sometimes very large. In one set of pilot plant experiments on hydrogenation of fatty oils, 1 gm palladium as 2% palladium-on-carbon reduced 545.000 gm oil to a satisfactory product (Zajcew, 1960).

Not infrequently the product changes somewhat when a catalyst is reused (Hartung and Chang, 1952; Skita and Rössler, 1939; Eliel and Ro, 1957; Farmer and Galley, 1933a,b; Haller and Schaffer, 1933; Mayo and Hurwitz, 1949). The change is often of the same type brought out by deliberate de-activation of the catalyst by addition of various inhibitors. A reused catalyst may give better results than a fresh catalyst (Gensler and Schlein, 1955), but not necessarily so. It would seem desirable in general research work not to reuse catalyst, for reuse may introduce an uncontrolled and irreproducible variable.

Catalyst Regeneration

Spent catalysts are regenerated usually by oxidation, by steam, by heat, by solvent extraction, or by various combinations thereof. The method of choice depends upon the cause of deactivation and on the equipment available for regeneration. A few examples from the literature will suffice to illustrate the general methods. No method is universally applicable and

apparently a procedure has to be worked out anew for each catalyst system. Poisoning and general methods of revivification have been discussed at length by Maxted (1951). It should be noted that restoration of the original catalyst activity is not in itself a sign of successful regeneration. The regenerated catalyst should in addition have an adequate life, which is by no means always the case.

1. Oxidation

Catalyst regeneration through oxidation may involve restitution of a catalyst to its original active form, as in oxidation of inactive platinum to active platinum oxide (Carothers and Adams, 1923), or conversion of strongly adsorbed inactivating materials to compounds more easily removed, as in oxidation of divalent sulfur, or actual burning off of carbonaceous deposits. The last type of regeneration may be accompanied by very large increases in temperature and the oxidation must be carefully controlled to avoid irreparable catalyst damage (Schulman, 1963).

Catalysts poisoned by various metal ions have been restored by treatment with an excess of an organic sulfide, which displaces the metal ions through mass action, followed by oxidation with hydrogen peroxide to convert the sulfur compound to nontoxic form (Maxted and Ali, 1962).

2. Steam

Catalysts may often be regenerated by treatment with wet or dry steam. Catalysts deactivated by use in an anthraquinone-hydrogen peroxide process were reactivated by treatment with wet steam containing about 10% water at 80–200°C (Jenny *et al.*, 1963). Platinum metals-on-carbon catalysts, deactivated in a vinyl ester process, were regenerated by treatment with superheated steam at 700–900°C (Japanese Patent 25,498/65).

3. Heat

If the deactivating adsorbed substances are sufficiently volatile, catalysts may be regenerated by heating. Rhodium catalysts deactivated during hydrogenation of anilines were reactivated by heating to 200–500°C for 4–24 hours (British Patent 906,858).

4. Solvent Extraction

Many spent catalysts may be restored by removal of strongly adsorbed deactivating species through extraction of the catalyst with an appropriate solvent. Spent palladium-on-carbon catalysts used in the selective hydrogenation of limonene, and deactivated through 30 reuses, were easily reactivated

by washing with acetone and drying for 1 hour at 110°C (Newhall, 1958). Alkali or dilute acid washes are used frequently in restoration of spent catalysts. For instance, a palladium-on-carbon catalyst spent from use in hydrogenation of butyrolactone was reactivated by washing with an alkaline solution and then with water, drying, and exposure to air (Kolyer, 1965). The appropriate solvent to be used can often be judged from the probable nature of the adsorbed deactivating species. Toxic metal ions may also be removed by solvent wash, to an extent that varies inversely with the temperature at which they were adsorbed (Maxted and Ali, 1962).

VII. INDUCTION PERIODS

Some reductions have induction periods, that is, some time is required before the maximum rate is obtained or before hydrogenation occurs at all. Ruthenium catalysts are particularly inclined to exhibit induction periods, especially at low pressures. The rate curve for a typical hydrogenation over ruthenium is shown in Fig. 1 (page 239). After almost an hour, hydrogen absorption began abruptly at nearly maximum rate. With this catalyst the induction period was eliminated completely by shaking the catalyst and solvent together with hydrogen for 1 hour before the substrate was added. The induction period was eliminated also by addition of 1 atom of stannous ion per atom of ruthenium.

The length of the induction periods appears to bear no relation to the activity of the catalysts. Induction periods with ruthenium catalysts seem to increase in length with age of the catalyst, but inasmuch as induction periods are highly variable it is difficult to establish a quantitative relationship. In our laboratory, induction periods of at least 1 hour have been observed over palladium, platinum, and ruthenium catalysts at atmospheric pressure. One reduction over 5% ruthenium-on-carbon absorbed no hydrogen in at least 7 hours; the reduction went to a successful completion sometime during the night. It would seem to be good practice never to abandon an apparently unsuccessful reduction too hastily.

PREREDUCTION

It is common practice to prereduce platinum metal catalysts; that is, the catalyst and solvent are shaken together with hydrogen before the substrate is added. One purpose of prereduction is to ensure that the measured hydrogen absorption arises only from absorption by the substrate. Another purpose is to activate the catalyst.

Prereductions are usually not necessary and are sometimes harmful. For instance, platinum oxide is inactive, or essentially so, for hydrogenation of aldehydes when it has been reduced to the metal (Willstätter and Jaquet, 1918). On the other hand, platinum oxide was shown to be catalytically inactive for reduction of nitro compounds; hydrogenation took place only over the reduced metal (Yao and Emmett, 1961). Many of the effects of pre-reduction of platinum oxide catalysts seem to be connected with its sodium content (Yao and Emmett, 1961).

In our laboratory, it is routine practice to prereduce ruthenium catalysts when they are to be used at low pressures. Hydrogenations over these catalysts are prone to show induction periods, which are sometimes lengthy and frequently erratic. A prereduction of 1 hour usually eliminates the induction period.

VIII. REPRODUCIBILITY OF CATALYSTS

The question of catalyst reproducibility cannot be separated from the criteria used to measure reproducibility. Catalysts may be compared with respect to density, hardness, content, surface area, selectivity, activity, poisoning resistance, etc. The usual and most useful criteria of reproducibility are related to some aspect of performance, for instance activity or selectivity. Another meaningful measure related to performance is resistance to poisoning, and another, in certain uses, is resistance to attrition. In any event it is a formidable task to ascertain whether two catalysts are identical.

One important factor tending to make catalysts reproducible is constancy of preparation, but this in itself is not an adequate guarantee of reproducibility inasmuch as all catalyst preparations are subject to various subtle and often unknown influences that alter catalyst quality. Wide variations in activity were found in "duplicate" palladium-on-carbon catalysts made by shaking a mixture of palladous chloride and charcoal in water with hydrogen (Young et al., 1953). Some catalyst preparations give much more consistent results than others, and the art of making "duplicate" catalysts is an important part of industrial know-how.

In practice it is poor policy to assume that duplicate catalysts are obtained from presumably identical preparations. All catalysts should be checked for activity, selectivity, or other meaningful criteria of performance.

IX. INHIBITORS AND POISONS

Platinum metal catalysts are subject to partial or total deactivation by many substances, including heavy metal ions, halides, divalent sulfur

compounds, carbon monoxide, amines, phosphine, etc. (Maxted, 1951), as well as, in some instances, by the substrate itself* (Smutny et al., 1960). Whether deactivation is partial or total often depends only on the quantity of the inhibitor. Catalyst inhibition may occur in various ways, as through blocking of the catalyst sites by overly strong adsorption (Maxted, 1951), by interaction of the inhibitor and substrate to alter the nature of the material undergoing hydrogenation (Adams et al., 1927), or by preventing conversion of the catalyst to an active form (Yao and Emmett, 1961). Partial catalyst deactivation may be accompanied by various favorable effects, such as increased selectivity. A catalyst modifier may therefore be simultaneously both an inhibitor and a promoter, the appropriate name being determined by the focus of interest.

A quantitative determination of the inhibiting effect of any substance is easily made by measuring the decrease in reaction rate when known quantities are added to the catalytic system (Maxted, 1951). Such measurements are of both theoretical and commercial interest (Montgomery et al., 1958; Greenfield, 1963). However, in most applications the nature of the inhibiting substances is never elucidated, nor need it be. When satisfactory methods of removing poisons from a reaction system have been found, or when, by proper choice of reaction conditions, formation of poisons is prevented, then the poisoning problem is, for practical purposes, solved. In fact, the nature of the inhibiting substances is often deduced from the types of procedure that were effective in their removal.

A. HALIDE IONS

Platinum metal catalysts may be strongly inhibited by halide ions, particularly iodide. Sodium fluoride, chloride, and bromide had little effect on the reduction of p-nitrotoluene over 5 % palladium-on-carbon, but sodium iodide caused severe poisoning (Greenfield, 1963). Sodium iodide was the most poisonous of the sodium halide salts for reduction of cinnamic acid over palladium-on-carbon (Isogai, 1960). Hydrofluoric acid and hydrochloric acid were promoters in hydrogenation of cinnamaldehyde over palladium-on-carbon; hydrobromic and hydroiodic acids were inhibitors (Rylander and Himelstein, 1964). Palladium-on-carbon was completely and irreversibly poisoned by iodide ion in hydrogenation of 2- or 4-stilbazole methiodides, but the reduction proceeded smoothly over platinum oxide in methanol (Phillips, 1950). Reduction of a complex acridizinium bromide over platinum oxide failed but, if the bromide were exchanged for chloride by passage through an anion-exchange resin, hydrogenation then proceeded readily.

* Inhibition of the catalyst by overly strong adsorption of the substrate may frequently be prevented by dropwise addition of the substrate to the reaction mixture.

The authors suggested alternatively that the success of the procedure may derive from removal of a small, quantity of phosphate ion rather than exchange of halogen (Bradsher and Berger, 1958).

It appears that inhibition of hydrogenation over platinum metal catalysts by halide ions usually increases with increasing molecular weight of the halogen. The extent of inhibition also depends on the substrate (Zakumbaeva and Sokol'skii, 1961) and the catalyst. Potassium halides are said to inhibit hydrogenation over platinum catalysts primarily by lowering the rate of hydrogen activation, while over palladium and nickel they lower the rate of activation of the unsaturated compound (Sokol'skii, 1964b).

B. Acids and Bases

Catalytic reductions are sometimes markedly affected by the presence of small quantities of acids or bases. Each may act as an inhibitor or a promoter in itself, or its influence may be due to counteracting the effect of the other. If an inhibiting base is a product of the reaction, an equivalent of acid or more may be needed. Traces of acids may affect reductions adversely if they catalyze homogeneous reactions that compete with the normal course of reduction. For instance, reduction of benzaldehyde over platinum oxide in technical methanol stopped at 70% of theoretical absorption. All the benzaldehyde had disappeared, but the unreduced portion had been converted to the dimethyl acetal by trace quantities of acid in the solvent (Carothers and Adams, 1924). Acids may affect activity adversely by promoting, especially in oxidizing media, solution of the catalytic metal. For example, the deactivation by hydrochloric acid of platinum catalysts used in the decomposition of hydrogen peroxide was attributed to partial solution of the platinum (Strel'nikova and Lebedev, 1963).

Many examples of promotion by acid may be attributed to counteracting the inhibiting effect of small quantities of alkali in platinum oxide catalysts, which evidently inhibit at least ring saturation (Keenan et al., 1954), ketone reduction (Phillips and Mentha, 1956), and hydrogenolysis of benzyl hydroxyl (Shriner and Witte, 1941). There is also sometimes a promoting effect of acids in reduction of aromatic rings over rhodium catalysts. Reduction of α-substituted benzyl alcohols to the corresponding cyclohexyl analogs over 5% rhodium-on-alumina in methanol proceeded more than twice as rapidly if 1% acetic acid were present. Hydrogenolysis of the hydroxyl function is evidently negligible, for mandelic acid afforded hexahydromandelic acid in 94% yield (Stocker, 1962). On the other hand, hydrochloric acid (in large quantities) was shown to be a strong inhibitor for reduction in methanol of benzoic acid or toluene over 5% rhodium-on-carbon or -alumina (Freifelder, 1961). Acetic acid in ethanol had a detrimental effect on reduction of aniline

to cyclohexylamine over rhodium-platinum catalyst. With no acetic acid, the yield of cyclohexylamine was 92 %, unaccompanied by dicyclohexylamine. With 1 % acetic acid, the yield dropped to 75 % and 12 % of dicyclohexylamine was formed (Nishimura and Taguchi, 1963).

Small amounts of sulfuric acid in palladium black catalysts are strong promoters for reduction of aliphatic-aromatic ketones. The catalytic activity is partly lost when the acid is removed, but can be restored by treatment with sulfuric acid (Kindler et al., 1949). This acid was also a specific promoter for reductions of 4-halo-2-acyl phenols to 4-halo-2-alkyl phenols over platinum black. The presence of sulfuric acid minimized unwanted dehydro-halogenation (Kindler et al., 1953).

C. METAL IONS

Metal cations of all types may cause severe inhibition of platinum metal catalysts, but there seems to be no way of generalizing just what effect the cations will have. Sodium and magnesium, usually not considered particularly toxic, were very objectionable at 60 parts per 1,000,000 parts of palladium in hydrogenation of rosin acids (Montgomery et al., 1958). Silver nitrate inhibited hydrogenation of acetophenone and octene-1 over platinum catalysts, whereas it was a strong promoter for hydrogenation of nitrobenzene over platinum (but not over palladium) (Rylander and Karpenko, 1966). Zinc acetate was a strong inhibitor for hydrogenation of nitrobenzene over platinum, but its effect was to a large extent counteracted when safrol was added to the system (Adams et al., 1927). These examples will suffice to show that the effect a heavy metal may have is contingent on the particular catalyst and also on the substrate. Many catalysts are deliberately inhibited by heavy metals, usually to increase selectivity. In any event it is safe to say that heavy metal ions in a catalytic system will have some sort of effect on the catalyst, and their presence is always something to be reckoned with.

D. OXYGEN

Small amounts of oxygen may function as either a promoter or inhibitor in catalytic hydrogenations. One might surmise that oxygen would have adverse effects in reductions where the substrate, intermediates, or products are easily oxidized, and where these oxidation products are catalyst inhibitors. For instance, traces of oxygen in reduction of N-nitrosodimethyl-amine over palladium-on-carbon cause catalyst deactivation and the use of deaerated water as a solvent is suggested (Feldman and Frampton, 1964). A successful reduction of pyrrole was achieved only by rigid exclusion of

oxygen (Hess, 1913); however, later workers used frequent oxygen regenera-
tions of the catalyst to achieve success (Andrews and McElvain, 1929).

The presence of oxygen might be expected to prove beneficial in reductions
where the active catalyst is oxygenated. The rationale for regeneration of
platinum oxide catalysts by oxygen is that platinum catalysts deprived of
oxygen are inactive (at least in certain reductions) (Tuley and Adams, 1925).
The activity of platinum-on-carbon and ruthenium-on-carbon, as well as
of platinum oxide, can be improved by periodic shaking with oxygen, when
these catalysts are used in hydrogenation of an aliphatic aldehyde. An
increase in catalytic activity may also be obtained by adding oxygen initially
to the hydrogen. These beneficial effects of oxygen are not general; oxygen
was an inhibitor in hydrogenation of octene and nitropropane (Rylander and
Kaplan, 1961). Oxygen (not over 0.5%) is said to improve catalyst activity
in vapor phase hydrogenation of benzoic acid to cyclohexane carboxylic
acid (Belgian Patent 608,776).

Platinum metals are often effective catalysts in oxidations as well as
hydrogenations. For this reason, and apart from the possibility of fire, it is
good practice to remove the catalyst from the reaction mixture when the
reaction is finished to avoid complications. For instance, 1,6-dimesitoyl-1-
cyclohexene absorbed one equivalent of hydrogen on reduction over platinum
oxide in absolute ethanol. But when the reaction mixture was exposed to air
an instantaneous, quantitative, catalytic oxidation occurred (Fuson, *et al.*,
1960).
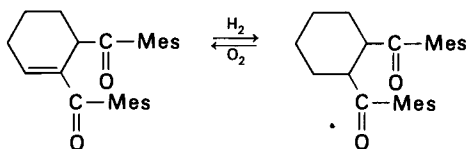
E. CARBON MONOXIDE AND CARBON DIOXIDE

Inhibition by carbon monoxide or by carbon dioxide is a problem of
considerable consequence in hydrogenation of certain organic compounds.
With suitable substrate large quantities of these materials may be formed
through decarbonylations or decarboxylations accompanying hydrogena-
tion. Palladium is in fact an excellent catalyst for decarbonylation of certain
aldehydes (Hoffman and Puthenpurackal, 1965; Hawthorne and Wilt, 1960;
Hoffman *et al.*, 1962). Extensive decarboxylation is apt to accompany
hydrogenation of certain carboxylic acids, for instance nicotinic acid, and
special techniques must be employed to prevent it (Freifelder and Stone,
1961); Freifelder, 1963). Decarboxylation may be both thermal and catalytic,

and its extent may vary with the catalyst; ruthenium caused more decarboxylation of rosin acids than rhodium or palladium. In this study of rosin acids, the efficiency of a catalyst for hydrogenation was found to be roughly inversely proportional to the amount of decarboxylation that it causes (Montgomery *et al.*, 1958). In another study, resistance to poisoning by carbon monoxide was found to depend on catalyst activity and the support. Palladium-on-carbon was more active and less sensitive to poisoning than palladium-on-barium sulfate, pumice, or kieselguhr (Rosenmund and Langer, 1923). Catalyst inhibition by carbon monoxide or carbon dioxide can be diminished by continuous or periodic venting of the reactor.

F. SULFUR COMPOUNDS

Platinum metal catalysts are strongly inhibited by compounds containing divalent sulfur. Oxidized sulfur, on the other hand, in a form not easily reduced, is nontoxic, and materials such as dimethyl sulfoxide and sulfuric acid may make excellent solvents for catalytic hydrogenations. Conversion of divalent sulfur to an oxidized form by treatment with an oxidizing agent is one way of rendering nontoxic feeds containing toxic sulfur. Oxidizing agents may also be used to detoxicate catalysts that have become inactive through sulfur poisoning (Maxted, 1951).

The relative toxicity of various sulfur compounds has been correlated with their structure and molecular weight (Maxted, 1951). In a practical situation, however, one does not choose the toxic impurities in a system, and in fact, except on rare occasions, one has no inkling of what they may be. If the toxicity of a system is moderately low it may be overcome by simply using more catalyst. But if this expedient fails, or if the amount of catalyst required is excessive, then some attempt must be made to detoxify the system. The methods of detoxication are numerous and a suitable one can usually be found. A method of wide applicability consists in stirring the reaction mixture with spent catalyst, with or without hydrogen present. After this treatment fresh catalyst may be added directly, or it may prove desirable to first remove the spent catalyst. A frequently used variation is to pretreat the reaction mixture with a base metal catalyst, such as Raney nickel. Treatment of the reaction mixture with an active absorbent, such as high surface carbon or alumina, may be sufficient for detoxification. Other treatments that have proved successful include shaking or refluxing the reaction mixture, when suitable, over sodium, zinc, nickel, sodium hydroxide, and magnesium oxide. Oxidizing agents, such as hydrogen peroxide or chromic acid, have also been used as detoxicants. These various treatments are often remarkably successful, but exactly what they accomplish usually remains unknown; the toxicants may well be other things besides sulfur compounds.

The presence of sulfur compounds is not always detrimental. Catalysts are frequently deactivated deliberately by sulfur compounds to increase selectivity, as in the well-known Rosenmund reduction of acid chlorides. Excellent results have been obtained by use of sulfided platinum or rhodium catalysts* in reductive alkylations of aromatic amines or in reduction of halonitroaromatics to amines, unaccompanied by dehydrohalogenation (Dovell and Greenfield, 1965). Traces of thiophene completely prevented hydrogenation of benzene over platinum without altering its activity for olefin hydrogenation (Foresti, 1951). Similarly, a 5% palladium-on-carbon catalyst inhibited by 7.5–9 mg thiophene per gm catalyst allowed selective hydrogenation of the ethylenic function of furfurylidenephenylacetonitrile (Belgian Patent 650,321). The addition of sulfur compounds in carefully adjusted amounts proved very useful in preventing hydrogenolysis of the benzyl oxygen during saturation of an olefin in an unsaturated benzyl ether over palladium (Oelschläger, 1960).

The problems of reduction in systems containing trace amounts of sulfur are exaggerated when the substrates themselves are sulfur compounds. Substrates containing divalent sulfur are usually difficult to hydrogenate. Nonetheless, many successful reductions of this type of compound have been carried out. High catalyst loadings are required and the reduction proceeds very slowly. Palladium-on-carbon is usually used in these reductions (Tarbell and McCall, 1952; Mozingo et al., 1945; Messina and Brown, 1952; Parham et al., 1953; Sheehan and Beck, 1955; Bolhofer et al., 1960), sometimes at elevated temperatures and pressures (Pines et al., 1951; Schneider et al., 1961; Weitkamp, 1959). Some reductions are apparently best carried out in alkaline solution (Bateman and Shipley, 1958; Johnston and Gallagher, 1963). Platinum oxide (Petropoulos et al., 1953) and ruthenium (Cope and Farkas, 1954; Vinton, 1949) have also been used with success.

X. PROMOTERS

Small quantities of various substances that have favorable effects on activity, selectivity, or catalyst life may be loosely termed promoters.†
In liquid phase hydrogenations, promoters are often the same types of material that are also inhibitors or, in larger quantities, poisons. Promotion is not an intrinsic property of the modifier and catalyst, but also depends critically on the substrate. What may prove to be a promoter with one substrate may be detrimental to another, and for this reason promotion is discussed under hydrogenation of the various functional groups.

* Manufactured by Engelhard Industries, Newark, N.J.
† For fine distinctions among various types of promoter, see Innes (1954).

XI. PREPARATION OF CATALYSTS

Catalyst preparation is an artful business, much of which is proprietary. The properties of a catalyst are determined by the total history of its preparation, which includes also the history of the ingredients, a point invariably disregarded in descriptions of catalyst preparation. Good reviews of catalyst preparation have been given by Ciapetta and Plank (1954) and by Innes (1954). The present discussion is intended only to exemplify general procedures and to point out various ways in which catalysts can be made, without attempting to evaluate the procedure or the resulting catalyst.

A. UNSUPPORTED CATALYSTS

Adams and Shriner (1923) carefully examined the factors affecting the activity of platinum oxide catalysts prepared by fusion of chloroplatinic acid with nitrates. A fusion temperature of about 500°C was most satisfactory for a catalyst of maximum activity and minimum lag (the time required to reduce platinum oxide to platinum black). Fusion with nitrates of lithium, potassium, calcium, barium, or strontium was not nearly so satisfactory as with sodium nitrate. The use of very pure chloroplatinic acid may give a less satisfactory catalyst in some reductions than catalysts prepared from less pure reagents (Carothers and Adams, 1923). Platinum oxides prepared by this fusion method are more active than those prepared by earlier procedures, and the fusion method, or variation thereof, has become a popular method of preparation. Platinum oxides prepared in this way usually contain residual sodium, which in some reactions has an adverse effect. The sodium can be removed by washing with dilute acid (Keenan *et al.*, 1954). A procedure has been described for preparation of a platinum oxide catalyst of reproducible activity, which involves the essentially instantaneous heating of platinic chloride to 520°C in the presence of sodium nitrate (Frampton *et al.*, 1951). Ammonium chloroplatinate has also been used in the sodium nitrate fusion (Bruce, 1936).* A technique for obtaining adequate temperature control in synthesis of platinum oxides has been described (Short, 1936); fusion is done in a 50-ml Pyrex beaker resting in the cavity of a copper block, heated by a ring burner. Activity is affected by fusion temperature, and several maxima at 160°, 220°, 250°, and 500°C were obtained on the curve of catalytic activity vs. calcination temperature (Strel'nikova *et al.*, 1956). Platinum catalysts may be stabilized by reduction of platinum oxide with hydrogen, washing with water, drying *in vacuo*, and treating with carbon dioxide (Yamanaka, 1959). The activity of platinum black for use in hydrogenation

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* An erratum appeared amending footnote 4 of this reference to read, "(4) The addition of a trace of $FeSO_4$ served to promote the reaction."

of carbon–carbon double bonds and carbonyl functions is said to be increased 2–3 times by heating the catalyst to 150–180°C under oxygen at 1000 psig (Laffitte and Grandadam, 1935). A method for preparation of platinum sponge (Willstätter and Hatt, 1912) was improved (Willstätter and Wald-schmidt-Leitz, 1921) through use of potassium hydroxide instead of sodium hydroxide. Solution of the less soluble potassium platinum salt proceeded more slowly, and foaming and sudden temperature rises were more easily avoided. A novel preparation of a platinum catalyst consists of heating platinum with a 10-fold mole excess of lithium above 500°C under an argon atmosphere, followed by hydrolysis (Nash et al., 1960). Some of these preparations are said to make highly effective catalysts for hydrogenation of olefins. An active palladium black, termed "S-catalyst," was prepared by treating a palladium black several times with 15% sulfuric acid, washing with water and then methanol, and heating (Kindler et al., 1949). Removal of about 5×10^{-6} mole of sulfuric acid from 0.5 gm catalyst by shaking with water and hydrogen caused a partial deactivation. Most of the lost activity could be regained by treating the deactivated catalyst with 0.0003 mole of sulfuric acid. The catalyst was strongly deactivated by treatment with trace amounts of sodium hydroxide. This catalyst was very much more active for reduction of acetophenone than that prepared by an earlier procedure (Willstätter and Waldschmidtt-Leitz, 1921). Borides of palladium, platinum, and rhodium were prepared from aqueous solutions of the metal chlorides and sodium or potassium borohydride. The catalysts are said to be more resistant to loss of activity through aging than are the simple blacks of the metals (Polkovnikov et al., 1962). Reduction of hexachloroplatinic acid with silicon hydride (Bott et al., 1962) gave a platinum catalyst said to be many times more active than that prepared by either sodium nitrate fusion or sodium borohydride reduction (Brown and Brown, 1962).

Tetrammineplatinum(II) bromide (Watt et al., 1953) and bromopentam-mineiridium(III) bromide (Watt and Mayfield, 1953) have been reduced with potassium in liquid ammonia at its boiling point to yield products that on decomposition, are active catalysts for reduction of allyl alcohol.

Palladous oxide may be prepared by fusion of palladous chloride and sodium nitrate (Shriner and Adams, 1924). Optimum fusion temperature is about 600°C. The melt is cooled, dissolved in water, and palladous oxide filtered off. Catalysts prepared in this way compare favorably with those made by other earlier techniques (Kern et al., 1925). It was found that the activity of palladium black, with respect to selective oxidation of hydrogen in carbon monoxide, decreased markedly in case alkali was either added in excess or exhaustively removed. The surface area of the catalysts decreases along with a decrease in alkali content (Soto and Ishizuka, 1958).

A preparation of a ruthenium catalyst involves fusion at 400°C of ruthenium metal powder, potassium hydroxide, and potassium nitrate.

The melt is dissolved in water, boiled with activated carbon, and ruthenium dioxide precipitated by addition of methanol. This catalyst, when suitably inhibited, is used for selective reduction of unsaturated aldehydes or ketones to unsaturated alcohols (Japanese Patent 25,654/63). Ruthenium catalysts prepared by reduction of ruthenium oxide at 80–100°C were more active than those reduced at either higher or lower temperatures (Takagi, 1963). Mixed rhodium–platinum oxide (Nishimura, 1960, 1961a,b) and platinum–ruthenium oxide catalysts (Bond and Webster, 1964) have been prepared by suitable modification of the sodium nitrate fusion method. The mixed catalysts are said to possess properties different from those of either metal alone.

Palladium and platinum catalysts have been prepared with synthetic high polymers as protective colloids (Rampino and Nord, 1941). Catalysts suitable for use in water or water–alcohol mixtures use polyvinyl alcohol or polyacrylic acid; for hydrogenations in organic solvents, polymethyl methacrylate or the methyl ester of polyacrylic acid can be used. A palladium catalyst can be made from a 2% aqueous solution of polyvinyl alcohol and palladium chloride by converting the palladium salt to the hydroxide with sodium carbonate and reducing with hydrogen. Other catalysts are made similarly. Divalent vanadium can be used for the reducing agent instead of hydrogen (Rampino and Nord, 1943). Iridium (Dunworth and Nord, 1950) and rhodium-on-polyvinyl alcohol (Hernandez and Nord, 1948) have also been prepared. The uses and mechanism of action of noble metal–synthetic polymer catalysts have been reviewed by Dunworth and Nord (1954). Palladium–platinum catalysts stabilized by gum arabic were prepared by Rideal (1920).

B. SUPPORTED CATALYSTS

All supported platinum metal catalysts are prepared by limitless variation of a few procedures (Innes, 1954), an object of which is to obtain metal or metal salt in highly dispersed form. A frequently used procedure involves precipitation of the catalytic metal onto a support by converting a solution of the metal to an insoluble form. One such preparation is 5% palladium-on-barium sulfate, in which palladium chloride is reduced to palladium by alkaline formaldehyde in the presence of finely divided barium sulfate. Palladium-on-barium carbonate, carbon (Mozingo, 1955), or strontium carbonate may be prepared similarly (Johnson et al., 1956).

$$Na_2PdCl_4 + CH_2O + 3NaOH \longrightarrow Pd + HCOONa + 4NaCl + 2H_2O$$
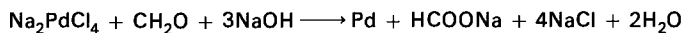
Hydrogen is often used as a reducing agent. Palladium-on-carbon, for instance, may be prepared by adding sodium acetate to a solution of

palladium chloride and shaking the mixture under hydrogen in the presence of carbon (Mozingo, 1955). Other suitable reducing agents are hydrazine (Paal and Amberger, 1904), sodium formate (Zelinsky and Glinka, 1911), and sodium borohydride (Brown and Brown, 1962). Platinum-on-carbon catalysts have been prepared by reducing with hydrogen chloroplatinic acid and a trace of palladium chloride in the presence of carbon (Baltzly, 1952).

Another common method of preparation involves impregnation. A 5% palladium-on-carbon, for instance, may be prepared in this way by evaporating a solution of palladium chloride in hydrochloric acid in the presence of carbon. The catalyst is dried and stored until needed. When it is to be used the catalyst is shaken with hydrogen, preferably in the solvent to be used in the hydrogenation (Mozingo, 1955). A 30% palladium hydroxide-on-strontium carbonate catalyst may be prepared by heating an aqueous solution of palladium chloride in the presence of strontium carbonate (Johnson et al., 1956).

REFERENCES

Adams, R., and Shriner, R. L., *J. Am. Chem. Soc.* **45**, 2171 (1923).
Adams, R., Cohen, F. L., and Rees, C. W., *J. Am. Chem. Soc.* **49**, 1093 (1927).
Adams, R., Voorhees, V., and Shriner, R. L. *In* "Organic Synthesis," Collected Vol. I, 2nd Ed., p. 465, Note No. 1. Wiley, New York, 1946.
Akabori, S., Sakurai, S., Izumi, Y., and Fujii, Y., *Nature* **178**, 323 (1956).
Akabori, S., Sakurai, S., Izumi, Y., and Fujii, Y., *Biokhimiya* **22**, 154 (1957).
Andrews, L. H., and McElvain, S. M., *J. Am. Chem. Soc.* **51**, 887 (1929).
Angyal, S. J., and McHugh, D. J., *J. Chem. Soc.* p. 3682 (1957).
Augustine, R. L., *J. Org. Chem.* **28**, 152 (1963).
Baer, E., Maurukas, J., and Russell, M., *J. Am. Chem. Soc.* **74**, 152 (1952).
Baltzly, R., *J. Am. Chem. Soc.* **74**, 4586 (1952).
Barnes, R. A., and Fales, H. M., *J. Am. Chem. Soc.* **75**, 975 (1953).
Bateman, L., and Shipley, F. W., *J. Chem. Soc.* p. 2888 (1958).
Beamer, R. L., Smith, J. D., Andrako, J., and Hartung, W. H., *J. Org. Chem.* **25**, 798 (1960).
Bolhofer, W. A., Sheehan, J. C., and Abrams, E. L. A., *J. Am. Chem. Soc.* **82**, 3437 (1960).
Bond, G. C., and Webster, D. E., *Proc. Chem. Soc.* p. 398 (1964).
Bott, R. W., Eaborn, C., Peeling, E. R. A., and Webster, D. E., *Proc. Chem. Soc.* p. 337 (1962).
Bradsher, C. K., and Berger, H., *J. Am. Chem. Soc.* **80**, 930 (1958).
Brown, H. C., and Brown, C. A., *J. Am. Chem. Soc.* **84**, 1494 (1962).
Bruce, W. F., *J. Am. Chem. Soc.* **58**, 687 (1936).
Butz, L. W., Gaddis, A. M., and Butz, E. W. J., *J. Am. Chem. Soc.* **69**, 924 (1947).
Carothers, W. H., and Adams, R., *J. Am. Chem. Soc.* **45**, 1071 (1923).
Carothers, W. H., and Adams, R., *J. Am. Chem. Soc.* **46**, 1675 (1924).
Ciapetta, F. G., and Plank, C. J., *Catalysis* **1**, 315 (1954).
Cope, A. C., and Farkas, E., *J. Org. Chem.* **19**, 385 (1954).
Dovell, F. S., and Greenfield, H., *J. Am. Chem. Soc.* **87**, 2767 (1965).
Dunworth, W. P., and Nord, F. F., *J. Am. Chem. Soc.* **72**, 4197 (1950).
Dunworth, W. P., and Nord, F. F., *Advan. Catalysis* **6**, 125 (1954).
Eliel, E. L., and Ro, R. S., *J. Am. Chem. Soc.* **79**, 5992 (1957).
Farmer, E. H., and Galley, R. A. E. *J. Chem. Soc.* p. 687 (1933a).

Farmer, E. H., and Galley, R. A. E. *Nature* **131**, 60 (1933b).

Feldman, J., and Frampton, O. D., U.S.Patent 3,129,263, Apr. 14, 1964.

Foresti, B., *Ann. Chim. (Rome)* **41**, 425 (1951).

Frampton, V. L., Edwards, J. D., Jr., and Henze, H. R., *J. Am. Chem. Soc.* **73**, 4432 (1951).

Freifelder, M., *J. Org. Chem.* **26**, 1835 (1961).

Freifelder, M., *J. Org. Chem.* **28**, 1135 (1963).

Freifelder, M., and Stone, G. R., *J. Org. Chem.* **26**, 3805 (1961).

Fuson, R. C., Hatchard, W. R., Kottke, R. H., and Fedrick, J. L., *J. Am. Chem. Soc.* **82**, 4330 (1960).

Gensler, W. J., and Schlein, H. N., *J. Am. Chem. Soc.* **77**, 4846 (1955).

Germain, J. E., Bourgeois, Y., and Rousseaux, *Bull. Soc. Chim. France* **3**, 521 (1961).

Greenfield, H., *J. Org. Chem.* **28**, 2434 (1963).

Gutsche, C. D., Bailey, D. M., Armbruster, C. W., Wendt, M. W., Kurz, J. L., Strohmayer, H. H., and Seligman, K. L., *J. Am. Chem. Soc.* **83**, 1404 (1961).

Haller, H. L., and Schaffer, P. S., *J. Am. Chem. Soc.* **55**, 3494 (1933).

Harris, S. A., and Folkers, K., *J. Am. Chem. Soc.* **61**, 1245 (1939).

Hartung, W. H., and Chang, Y.-T., *J. Am. Chem. Soc.* **74**, 5927 (1952).

Hawthorne, J. O., and Wilt, M. H., *J. Org. Chem.* **25**, 2215 (1960).

Hayashi, E., and Nagao, T., *Yakugaku Zasshi* **84** (2), 198 (1964).

Hernandez, L., and Nord, F. F., *J. Colloid Sci.* **3**, 363 (1948).

Hess, K., *Chem. Ber.* **46**, 3125 (1913).

Hoffman, N. E., and Puthenpurackal, T., *J. Org. Chem.* **30**, 420 (1965).

Hoffman, N. E., Kanakkanatt, A. T., and Schneider, R. F., *J. Org. Chem.* **27**, 2687 (1962).

Innes, W. B., *Catalysis* **1**, 245 (1954).

Isogai, K., *Nippon Kagaku Zasshi* **81**, 792 (1960).

Jenny, T. M., Porter, D. H., and Zdrojewski, E. M., U.S. Patent 3,112,278, Nov. 26, 1963.

Johnston, T. P., and Gallagher, A., *J. Org. Chem.* **28**, 1305 (1963).

Johnson, W. S., Rogier, E. R., Szmuszkovicz, J., Hadler, H. I., Ackerman, J., Bhattacharyya, B. K., Bloom, B. M., Stalmann, L., Clement, R. A., Bannister, B., and Wynberg, H., *J. Am. Chem. Soc.* **78**, 6289 (1956).

Karpenko, I., Unpublished observations, Engelhard Ind., 1964.

Keenan, C. W., Giesemann, B. W., and Smith, H. A., *J. Am. Chem. Soc.* **76**, 229 (1954).

Kern, J. W., Shriner, R. L., and Adams, R., *J. Am. Chem. Soc.* **47**, 1147 (1925).

Kindler, K., Schärfe, E., and Henrich, P., *Ann. Chem. Liebigs* **565**, 51 (1949).

Koch, J. H., Jr., U.S. Patent 3,055,840, Sept. 25, 1962.

Koch, J. H. Jr., U.S. Patent 3,183,278, May 11, 1965.

Kolyer, J. M., U.S.Patent 3,214,385, Oct. 26, 1965.

Laffitte, P., and Grandadam, P., *Compt. Rend.* **200**, 456 (1935).

McElvain, S. M., and Adams, R., *J. Am. Chem. Soc.* **45**, 2738 (1923).

McQuillin, F. J., Ord, W. O., and Simpson, P. L., *J. Chem. Soc.* p. 5996 (1963).

Mariella, R. P., and Belcher, E. P., *J. Am. Chem. Soc.* **73**, 2616 (1951).

Mariella, R. P., and Havlik, A. J., *J. Am. Chem. Soc.* **74**, 1915 (1952).

Maxted, E. B. *Advan. Catalysis* **3**, 129 (1951).

Maxted, E. B., and Ali, S. I., *J. Chem. Soc.* p. 4137 (1961).

Maxted, E. B., and Ali, S. I., *J. Chem. Soc.* p. 2796 (1962).

Maxted, E. B., and Elkins, J. S., *J. Chem. Soc.* p. 5086 (1961).

Mayo, F. R., and Hurwitz, M. D., *J. Am. Chem. Soc.* **71**, 776 (1949).

Messina, N., and Brown, E. V., *J. Am. Chem. Soc.* **74**, 920 (1952).

Montgomery, J. B., Hoffmann, A. N., Glasebrook, A. L., and Thigpen, J. l., *Ind. Eng. Chem.* **50**, 313 (1958).

Mozingo, R., *In* "Organic Syntheses," Collected Vol. 3, p. 685. Wiley, New York, 1955.

Mozingo, R., Harris, S. A., Wolf, D. E., Hoffhine, C. E., Jr., Easton, N. R., and Folkers, K.,
  J. Am. Chem. Soc. **67**, 2092 (1945).
Nash, C. P., Boyden, F. M., and Whittig, L. D., *J. Am. Chem. Soc.* **82**, 6203 (1960).
Newhall, W. F., *J. Org. Chem.* **23**, 1274 (1958).
Nishimura, S., *Bull. Chem. Soc. Japan* **33**, 566 (1960).
Nishimura, S., *Bull. Chem. Soc. Japan* **34**, 32 (1961a).
Nishimura, S., *Bull. Chem. Soc. Japan* **34**, 1544 (1961b).
Nishimura, S., and Taguchi, H., *Bull. Chem. Soc. Japan* **36** (7), 873 (1963).
Oelschläger, H., *Arch. Pharm.* **293**, 442 (1960).
Overberger, C. G., and Lapkin, M., *J. Am. Chem. Soc.* **77**, 4651 (1955).
Paal, C., and Amberger, C., *Chem. Ber.* **37**, 124 (1904).
Parham, W. E., Roder, T. M., and Hasek, W. R., *J. Am. Chem. Soc.* **75**, 1647 (1953).
Petropoulos, J. C., McCall, M. A., and Tarbell, D. S., *J. Am. Chem. Soc.* **75**, 1130 (1953).
Phillips, A. P., *J. Am. Chem. Soc.* **72**, 1850 (1950).
Phillips, A. P., and Mentha, J., *J. Am. Chem. Soc.* **78**, 140 (1956).
Pines, H., Kvetinskas, B., Vesely, J. A., and Baclawski, E., *J. Am. Chem. Soc.* **73**, 5173 (1951).
Polkovnikov, B. D., Balandin, A. A., and Taber, A. M., *Dokl. Akad. Nauk SSSR* **145**, 809
  (1962).
Rampino, L. D., and Nord, F. F., *J. Am. Chem. Soc.* **63**, 2745 (1941).
Rampino, L. D., and Nord, F. F., *J. Am. Chem. Soc.* **65**, 429 (1943).
Rebenstorf, M. A., *Proc. Conf. Catalytic Hydrogenation Analogous Pressure Reactions, New
  York, June, 1966.*
Rideal, E. K., *J. Am. Chem. Soc.* **42**, 749 (1920).
Rosenmund, K. W., and Langer, G., *Chem. Ber.* **56B**, 2262 (1923).
Rylander, P. N., and Cohn, G., *Actes Congr. Intern. Catalyse, 2e, Paris, 1960* Vol. 1, p. 977.
  Editions Technip, Paris, 1961.
Rylander, P. N., and Himelstein, N., *Engelhard Ind. Tech. Bull.* **4**, 131 (1964).
Rylander, P. N., and Kaplan, J., *Engelhard Ind. Tech. Bull.* **2**, 48 (1961).
Rylander, P. N., and Karpenko, I., U.S. Patent 3,253,039, May 24, 1966.
Rylander, P. N., and Koch, J. H., Jr., U.S. Patent 3,177,258, Apr. 6, 1965.
Rylander, P. N., Rakoncza, N., Steele, D., and Bolliger, M., *Engelhard Ind. Tech. Bull.* **4**,
  95 (1963).
Rylander, P. N., Kilroy, M., and Coven, V., *Engelhard Ind. Tech. Bull.* **6**, 11 (1965).
Sabatier, P. "Catalysis in Organic Chemistry" (translated by E. E. Reid). Van Nostrand,
  Princeton, New Jersey, 1923.
Schneider, H. J., Bagnell, J. J., and Murdock, G. C., *J. Org. Chem.* **26**, 1987 (1961).
Schulman, B. L., *Ind. Eng. Chem.* **55**, No. 12, 44 (1963).
Sheehan, J. C., and Beck, C. W., *J. Am. Chem. Soc.* **77**, 4875 (1955).
Short, W. F., *J. Soc. Chem. Ind. (London)* **55**, 14T (1936).
Shriner, R. L., and Adams, R., *J. Am. Chem. Soc.* **46**, 1683 (1924).
Shriner, R. L., and Witte, M., *J. Am. Chem. Soc.* **63**, 2134 (1941).
Siegel, S., and Dmuchovsky, B., *J. Am. Chem. Soc.* **86**, 2192 (1964).
Skita, A., *Chem. Ber.* **45**, 3312 (1912).
Skita, A., and Rössler, R., *Chem. Ber.* **72B**, 265 (1939).
Smith, G. V., and Burwell, R. L., Jr., *J. Am. Chem. Soc.* **84**, 925 (1962).
Smutny, E. J., Caserio, M. C., and Roberts, J. D., *J. Am. Chem. Soc.* **82**, 1793 (1960).
Sokol'skii, D. V., "Hydrogenations in Solutions," p. 25. Davey, New York, 1964a.
Sokol'skii, D. V., "Hydrogenation in Solutions," p. 287. Davey, New York, 1964b.
Soto, T., and Ishizuka, K., *J. Res. Inst. Catalysis, Hokkaido Univ.* **6**, 138 (1958).
Stocker, J. H., *J. Org. Chem.* **27**, 2288 (1962).

Strel'nikova, Zh. V., and Lebedev, V. P., *Kataliticheskie Reaktsii v Zhidkoi Faze, Akad. Nauk Kaz. SSR, Kazakhsk. Gos. Univ. Kazakhsk. Resp. Pravlenie Mendeleevskogo Obshchestva, Tr. Vses. Konf., Alma-Ata, 1962* p. 304. 1963.

Strel'nikova, Zh. V., Lopatkin, A. A., and Lebedev, V. P., *Zh. Fiz. Khim.* **30**, 196 (1956).

Takagi, Y., *Sci. Papers Inst. Phys. Chem. Res. (Tokyo)* **57**, 105 (1963).

Tarbell, D. S., and McCall, M. A., *J. Am. Chem. Soc.* **74**, 48 (1952).

Tuley, W. F., and Adams, R., *J. Am. Chem. Soc.* **47**, 3061 (1925).

Vandenheuvel, F. A., *Anal. Chem.* **28**, 362 (1956).

Vinton, W. H., U.S. Patent 2,483,447, Oct. 4, 1949.

Watt, G. W., and Mayfield, P. I., *J. Am. Chem. Soc.* **75**, 6178 (1953).

Watt, G. W., Walling, M. T., Jr., and Mayfield, P. I., *J. Am. Chem. Soc.* **75**, 6175 (1953).

Weitkamp, A. W., *J. Am. Chem. Soc.* **81**, 3437 (1959).

Wilbert, G., and Sosis, P., U.S. Patent 3,028,429, Apr. 3, 1962.

Willstätter, R., and Hatt, D., *Chem. Ber.* **45**, 1471 (1912).

Willstätter, R., and Jaquet, D., *Chem. Ber.* **51**, 767 (1918).

Willstätter, R., and Waldschmidt-Leitz, E., *Chem. Ber.* **54B**, 113 (1921).

Wright, W. B., Jr., *J. Org. Chem.* **24**, 1016 (1959).

Yamanaka, T., Japanese Patent 2570/59, Apr. 17, 1959.

Yao, H. C., and Emmett, P. H., *J. Am. Chem. Soc.* **83**, 799 (1961).

Young, J. G., and Hartung, W. H., *J. Org. Chem.* **18**, 1659 (1953).

Young, J. G., Hartung, W. H., and Daniels, H. H., *J. Org. Chem.* **18**, 229 (1953).

Zajcew, M., *J. Am. Oil Chemists Soc.* **35**, 475 (1958).

Zajcew, M., *J. Am. Oil Chemists' Soc.* **37**, 11 (1960).

Zakumbaeva, G. D., and Sokol'skii, D. V., *Tr. Inst. Khim. Nauk, Akad. Nauk Kaz. SSR* **7**, 3 (1961).

Zelinsky, N., and Glinka, N., *Chem. Ber.* **44**, 2305 (1911).

2

Hydrogenation Reactors

All hydrogenation reactors serve the purpose of bringing hydrogen, the catalyst, and the substrate into contact in the absence of air. Some sort of mixing is provided to increase the rate of contact between the reactants and catalyst, and to increase the rate of diffusion of the products away from the catalyst surface. Reactors are also provided with some device to remove air from the system before hydrogen is introduced. Air is removed usually by evacuating the system and/or sweeping the reactor with an inert gas.

I. ATMOSPHERIC PRESSURE REACTORS

Reactors for hydrogenation at atmospheric pressure may be improvised readily. A flask equipped with a gas diffusor and a vent line is useful when it is desirable to examine the off-gas, as in hydrogenation of carbobenzyloxy groups or acid chlorides. Flasks may also be equipped with dropping funnels to add the substrate portionwise, or with reflux condensers or knock-backs to return all or a portion of a refluxing product to the flask. Detailed directions for carrying out a Rosenmund reduction in a three-necked flask equipped with ground joints, a stirrer, and reflux condenser have been given by Hershberg and Cason (1955) in *Organic Syntheses*.

A more generally used system consists of a glass reaction flask attached to a water burette and provided with stopcocks that permit evacuation of air from the system prior to introduction of hydrogen. Agitation is provided by a magnetic stirring bar or, better, by shaking the reaction flask. Numerous variations of this basic system have been described (Joshel, 1943; Morritz *et al.*, 1953; Fieser and Hershberg, 1938; Meschke and Hartung, 1960; Noller and Barusch, 1942; Frampton *et al.*, 1951). The reduction proceeds at constant pressure, and the rate and extent of hydrogenation are followed by measuring with a leveled water burette the decrease in system volume from time to time. Since the gas above the water in the burette is presumably

saturated, the actual hydrogen partial pressure is less than 1 atm and the measured gas volume change should be corrected accordingly. Other liquids can be used in the burettes as well as water; mercury-filled burettes may prove desirable when hydrogenations are carried out at low temperatures (Nickon and Bagli, 1961).

II. LOW PRESSURE REACTORS

Apparatus for carrying out hydrogenations at several atmospheres of pressure may be readily constructed (Adams and Voorhees, 1932; Snyder et al., 1957). However, the most commonly used low pressure apparatus is the commercial Parr hydrogenator (manufactured by the Parr Instrument Co., Moline, Illinois). The apparatus is recommended for hydrogenations not exceeding 60 psig or 100°C. Heavy-walled 500-ml Pyrex glass bottles are usually used, but adapters can be had for 250-, 1000-, and 2000-ml bottles. The bottles are held in place by a sturdy clamp in a motor-driven shaker mechanism and are connected to a 4-liter hydrogen reservoir equipped with two pressure gauges. One gauge indicates the gas pressure in the reaction bottle and the other the supply pressure in the hydrogen tank. As the reduction proceeds the pressure in the tank falls and the moles of hydrogen absorbed may be calculated from the pressure drop. Some models are supplied with electric heaters that heat the base of the reaction bottle. Buck and Jenkins (1929) modified this apparatus to work with 0.005–0.01 mole of substrate by inserting a needle valve between the bottle and hydrogen tank. With the valve closed only the hydrogen in the bottle was available for reduction. Russotto (1964) has suggested using machined polytrifluoro-chloroethylene stoppers sealed in the bottle with a sleeve of thin poly-tetrafluoroethylene instead of the conventional stoppers.

Reductions may be conducted and followed at constant pressure, if hydrogen enters the hydrogenation vessel from an external reservoir through a Dome regulator. The absorption of hydrogen is calculated from the pressure decrease in the external reservoir. Engelhard Industries markets an automatic hydrogen control unit that delivers hydrogen at constant pressure to the reactor while tracing out a permanent record of hydrogen consumption on a recorder chart. By use of limit switches on the recorder the gas supply can be switched off after absorption of a pre-set volume of gas.

Kasman (1965) of Polaroid Corporation has devised a compact multiple hydrogenator that permits hydrogenation of twelve samples simultaneously. The apparatus consists of a manifold that bears twelve pressure gauges, a box partitioned into a dozen bottle compartments strung with neoprene tubing to cushion the bottles, and a shaker on which the box is mounted. The manifold is bent in a U and contains twelve threaded stainless sockets

welded in at the closest spacing permitted by the gauge. Beyond the weld is a toggle switch, a connection to the bottle, a second toggle switch, and the pressure gauge. Each bottle is connected to its gauge with clear vinyl tubing. In operation, each bottle is charged with catalyst, solvent, and substrate, inserted in its compartment, and connected to its gauge. To protect the gauges, the upper valves are closed when the system is evacuated. The lower valves can be opened in any combination to connect the corresponding bottles to the manifold for evacuation, purging with nitrogen, or pressurizing with hydrogen. When all the bottles are charged, the lower toggle valves are closed to isolate each bottle with its gauge from the rest of the system. The void volume of each bottle is its hydrogen reservoir, and, if larger samples are hydrogenated, it is necessary to recharge the bottle with hydrogen from time to time.

III. MICROREACTORS

A number of investigators have described equipment suitable for hydrogenation of small quantities of material (Weygand and Werner, 1937; Cheronis and Levin, 1944; Vandenheuvel, 1952; Pack et al., 1952; Clauson-Kaas and Limborg, 1947), based on measurement of volume change at constant pressure. An apparatus with an accuracy of $\pm 2\%$, based on the principle of measuring a change in pressure at constant volume, has been described in detail by Hyde and Scherp (1930).

Hydrogen absorption has also been measured from the electrical current used to make electrically generated hydrogen (Miller and DeFord, 1958), and from the quantity of sodium borohydride solution consumed in producing hydrogen (Brown et al., 1963). A microhydrogenation technique for volatile compounds has been described by Engelbrecht (1957). Ogg and Cooper (1949) developed a simple magnetically stirred apparatus. A particularly simple system to construct, giving values on 10 mg steroids to $\pm 2\%$ without a thermostat, has been described by Harrison and Harrison (1964). Compounds difficult to reduce may be hydrogenated under pressure (Gould and Drake, 1951). Southworth (1956) converted a standard Burgess–Parr apparatus to an apparatus intermediate between analytical and preparative organic hydrogenators. A good discussion of equipment and technique for quantitative microhydrogenation has been given by Siggia (1963).

Microreactors combined with chromatographic technique provide an interesting way of studying catalytic reactions in packed columns. Small quantities (0.03 ml) of substrate are injected as liquids through a serum cap into a hydrogen stream, passed over the catalyst, and the effluent led directly into a chromatographic column (Kokes et al., 1955). The technique is particularly suited for giving information about the behavior of catalysts in the

first fraction of a second of exposure (Emmett, 1959). Steady state with respect to the catalyst may not be reached by this pulsing technique and the results may prove misleading (Carberry, 1964).

IV. HIGH PRESSURE REACTORS

Good general descriptions of high pressure hydrogenation reactors have been given by Adkins (1937) and by Komarewsky *et al.* (1956). More recently Bowen (1966), Rebenstorf (1966), and Blackburn (1966) have each discussed various aspects of safety, design, and control of pressure processing.* High pressure processing requires specially constructed reactors and equipment, and it is in precisely this area that commercial suppliers have been most active. Abundant literature, expert advice, and equipment of all kinds and sizes can be readily obtained from manufacturers. Some companies will design and build complete packaged units including instrumentation.

REFERENCES

Adams, R., and Voorhees, V., *In* "Organic Syntheses," Collected Vol. I, p. 61. Wiley, New York, 1932.

Adkins, H., "Reactions of Hydrogen." Univ. of Wisconsin Press, Madison, Wisconsin, 1937.

Blackburn, D. W., *Proc. Conf. Catalytic Hydrogenation Analogous Pressure Reactions, New York, June, 1966.* *

Bowen, J. C., *Proc. Conf. Catalytic Hydrogenation Analogous Pressure Reactions, New York, June, 1966.* *

Brown, H. C., Sivasankaran, K., and Brown, C. A., *J. Org. Chem.* **28**, 214 (1963).

Buck, J. S., and Jenkins, S. S., *J. Am. Chem. Soc.* **51**, 2163 (1929).

Carberry, J. J., *Ind. Eng. Chem.* **56**, No. 11, 39 (1964).

Cheronis, N. D., and Levin, N., *J. Chem. Educ.* **21**, 603 (1944).

Clauson-Kaas, N., and Limborg, F., *Acta Chem. Scand.* **1**, 884 (1947).

Emmett, P. H., *J. Phys. Chem.* **63**, 449 (1959).

Engelbrecht, R. M., *Anal. Chem.* **29**, 1556 (1957).

Fieser, L. F., and Hershberg, E. B., *J. Am. Chem. Soc.* **60**, 940 (1938).

Frampton, V. L., Edwards, J. D., Jr., and Henze, H. R., *J. Am. Chem. Soc.* **73**, 4432 (1951).

Gould, C. W., and Drake, H. J., *Anal. Chem.* **23**, 1157 (1951).

Harrison, I. T., and Harrison, S., *Chem. Ind. (London)* p. 834 (1964).

Hershberg, E. B., and Cason, J., *In* "Organic Syntheses," Collected Vol. III, p. 627. Wiley, New York, 1955.

Hyde, J. F., and Scherp, H. W., *J. Am. Chem. Soc.* **52**, 3359 (1930).

Joshel, L. M., *Ind. Eng. Chem. Anal. Ed.* **15**, No. 9, 590 (1943).

Kasman, S., Personal communication, 1965.

Kokes, R. J., Tobin, H., Jr., and Emmett, P. H., *J. Am. Chem. Soc.* **77**, 5860 (1955).

Komarewsky, V. I., Riesz, C. H., and Morritz, F. L., *In* "Technique of Organic Chemistry," (Weissberger, A., ed.) Vol. II, 2nd Ed., pp. 18–93. Wiley (Interscience), New York, 1956.

Meschke, R. W., and Hartung, W. H., *J. Org. Chem.* **25**, 137 (1960).

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* These lectures have been published by the New York Academy of Sciences.

Miller, J. W., and DeFord, D. D., *Anal. Chem.* **30**, 295 (1958).

Morritz, F. L., Lieber, E., and Bernstein, R. B., *J. Am. Chem. Soc.* **75**, 3116 (1953).

Nickon, A., and Bagli, J. F., *J. Am. Chem. Soc.* **83**, 1498 (1961).

Noller, C. R., and Barusch, M. R., *Ind. Eng. Chem. Anal. Ed.* **14**, No. 11, 907 (1942).

Ogg, C. L., and Cooper, F. J., *Anal. Chem.* **21**, 1400 (1949).

Pack, F. C., Planck, R. W., and Dollear, F. G., *J. Am. Oil Chemists' Soc.* **29**, 227 (1952).

Rebenstorf, M. A., *Proc. Conf. Catalytic Hydrogenation Analogous Pressure Reactions, New York, June, 1966.*

Russotto, P. T., *Chemist-Analyst* **53** (3), 85 (1964).

Siggia, S., "Quantitative Organic Analysis," 3rd Ed., pp. 318–341. Wiley, New York, 1963.

Snyder, J. R., Hagerty, P. F., and Molstad, M. C., *Ind. Eng. Chem.* **49**, 689 (1957).

Southworth, B. C., *Anal. Chem.* **28**, 1611 (1956).

Vandenheuvel, F. A., *Anal. Chem.* **24**, 847 (1952).

Weygand, C., and Werner, A., *J. Prakt. Chem.* **149**, 330 (1937).

3

Reaction Conditions

The successful outcome of a catalytic hydrogenation depends upon the propitious choice of a number of factors. Foremost among these is the proper choice of a catalyst, a choice most easily made by uncovering a suitable precedent. Other factors that include temperature, pressure, agitation, amount of catalyst, mode of addition, and solvent may also have a decisive influence. Fortunately, acceptable results can often be obtained throughout such a wide range of conditions that, unless there is a need to optimize a process, little attention need be given to these factors. But when the most appropriate catalyst is already in use and the reduction still fails in some respect, it is only through a change in process conditions that a satisfactory result can be obtained. An unavoidable complication in an examination of the effect of process variables on the outcome of a reduction is the fact that "the most appropriate catalyst" is not necessarily invariable, but may itself change with a change in process conditions.

I. TEMPERATURE

Usually but not always, as the temperature of hydrogenation is increased the rate is increased, and accordingly more efficient use may be made of the catalyst and equipment. Also there are some reductions that occur only at elevated temperatures. Offsetting these important advantages in operating at elevated temperatures are the possibilities:

(1) The catalyst may deactivate more rapidly.
(2) Selectivity may be less.
(3) The reactants or products may be thermally unstable.
(4) More side-reactions may occur.
(5) A different major product may be obtained.

Some reductions seem to have a temperature threshold, i.e., a temperature below which no reduction will occur. For instance, the hydrogenation of a

number of pyridines over palladium in acetic acid was successfully achieved
at 70–80°C, whereas no reduction whatever was observed at room tempera-
ture (Walker, 1962). A more striking example occurred in reduction of a
furoquinoline; a successful reduction was achieved at 54°C, while no re-
duction occurred at temperatures below 50°C (Huffman and Browder, 1964).
In view of these and many other examples, it would seem to be sound practice
to raise the reaction temperature before abandoning a reduction that either
failed entirely or was too sluggish to be useful.

Raising the temperature in reductions, which were already successful at
room temperature, need not necessarily be advantageous. The rate of hydro-
genation of 2-butyne-1,4-diol in dimethylformamide passes through a
maximum at 36°C, hydrogen solubility being a limiting factor (Tsybina and
Mokhova, 1964). An increased reaction temperature may cause side-
reactions to become prohibitively important (Tuley and Adams, 1925) or
cause catalyst deactivation. For instance, the rate of reduction of furfural
over platinum oxide in ethanol increased steadily with increasing tempera-
ture in the range 0–60°C, but, inasmuch as the rate of catalyst deactivation
was highest at 60°C, it was found most convenient to work at 40°C (Pierce
and Parks, 1929). Similarly, the rate of reduction of nitriles over platinum
oxide in acetic anhydride was very rapid in the range 50–100°C, but the
catalyst was poisoned before reduction was complete. Optimum tempera-
tures were judged to be 30–50°C (Carothers and Jones, 1925). Reduction of
p-methoxyphenol over 5% rhodium-on-alumina in ethanol proceeded to
complete saturation at room temperature, but stopped uncompleted when
the reduction was carried out at 60°C (Himelstein, 1964). Optimum tempera-
tures may vary with the catalyst. In the reduction of nitrosodimethylamine
the optimum temperature was 45–60°C over 5% palladium-on-carbon, but
25–30°C over 5% rhodium-on-carbon (Smith and Thatcher, 1962). In this
reduction the yield was influenced strongly by the temperature, and higher
temperatures were unfavorable for both catalysts, particularly rhodium,
because hydrogenolysis of the nitrogen–nitrogen bond became prominent.

The effect of temperature on the rate of reduction may vary with the
catalyst. For instance, in hydrogenation of soybean oil over 5% palladium-,
5% platinum-, and 5% rhodium-on-carbon, the rate over platinum and
rhodium was found to be less temperature-dependent than over palladium
(Riesz and Weber, 1964) (see Table I).

Presumably it would be easier to maintain a constant rate by raising the
temperature, as the catalyst deactivated with use in this reduction, when the
catalyst is palladium than when it is rhodium or ruthenium. In theory, a
constant activity can be maintained most easily through raising the tempera-
ture with those catalysts whose apparent activation energy is highest. On
the other hand, the rate of deactivation will vary with the temperature and
also with the catalyst. Just how many times a catalyst can be reused, and

TABLE I

EFFECT OF TEMPERATURE ON RATE OF HYDROGENATION OF SOYBEAN OIL[a]

Catalyst	Rate (mmoles/minute)	
	35°C	100°C
5% Pd/C	0.36	0.97
5% Pt/C	0.28	0.51
5% Rh/C	0.27	0.57

[a] Metal concentration based on oil = 0.025%.

how much its effective life may be extended by raising the temperature, need to be ascertained experimentally for each system. The possibility that initial activity can be partially or completely restored by operating at an increased temperature offers the possibility that the effective catalyst life may be appreciably extended.

The fact that the reduction rate often increases with an increase in reduction temperature, and sometimes the increase is marked, carries with it an inherent danger. Once a reduction has begun, the exothermic heat of hydrogenation drives the temperature higher with a consequent increase in rate of reduction and rate of heat liberation, etc. This cycle once begun can be difficult to stop and can result in loss of product, catalyst deactivation, or worse. In batch type of operation the reduction can usually be brought quickly under control by stopping the agitation.

EFFECT ON PRODUCT

In many hydrogenations the product varies with the reaction temperature. In general, hydrogenation at lower temperatures is less extensive and less random than reduction at higher temperatures. The percentage of *cis* isomers derived from reduction of ring compounds is usually greater at lower temperatures: *cis*-pinane from hydrogenation of α-pinene decreased from 80% at 0°C to 48.5% at 138°C (Cocker *et al.*, 1966); *cis*-dimethylcyclohexane from reduction of *p*-xylene decreased from 86.2% at 15°C to 56.1% at 160°C (Rylander and Steele, 1962). Hydrogenolysis increases with temperature and is minimized at lower temperatures (Nickon and Bagli, 1961; Walker, 1958; Smith and Stump, 1961). Partial hydrogenation of a function is sometimes effected conveniently at diminished temperature; cyclohexylhydroxylamine was obtained by hydrogenation of nitrocyclohexane at 10–20°C (Meister and Franke, 1959). Secondary amine formation during hydrogenation of nitriles is minimized by reduction at 14°C, higher temperatures favor

secondary amines (Young, 1958). Hydrogenations at reduced temperatures may prove advantageous when either the substrate or product is temperature-sensitive. Reduction of the nitroacetate (I) over 5% palladium-on-carbon in methanol at room temperature gave an impure product. The authors thought it likely that the newly formed aromatic amino group had been transacetylated by one of the acetamido groups of the pyrimidine ring. Accordingly, they subsequently conducted the hydrogenation at 0–15°C and obtained a good yield of II (DeGraw et al., 1961).
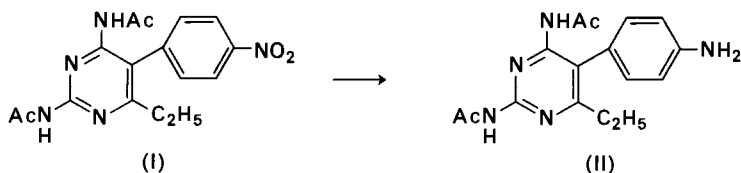
II. AMOUNT OF CATALYST

The important question of how much catalyst should be used arises in every problem. The amount of catalyst affects the rate, sometimes the product, and in commercial operation the economics of the process. The choice available covers extreme ranges; successful hydrogenations have been carried out with amounts of catalyst based on substrate ranging from a very small fraction of a percent to several hundred percent. Frequently a convenient amount of catalyst for a laboratory preparation under mild conditions is 1–5% of 5% metal-on-carrier based on the weight of substrate. This is more catalyst than would often be needed, but allows, in part, for the effect of accidental poisons and for an improper choice of solvent. The amount of catalyst can be subsequently lowered as optimum conditions are found. Cottonseed oil hydrogenations, for instance, are conveniently made with 0.01% of 5% palladium-on-carbon.

The guide is stated in terms of the commonly used 5% concentration of metal. If the metal concentration is appreciably different, or if an unsupported catalyst is used, an adjustment should be made accordingly. Beyond this, the guide should be tempered by judgment. Easily reduced functions, such as unhindered olefins or nitro groups, need relatively little catalyst for convenient rates; functions reduced with more difficulty need more catalyst. Compounds containing divalent sulfur will generally require very high catalyst loading levels. In any event, in preliminary tests it is certainly less aggravating to err on the side of having too much catalyst rather than too little.

The effect of the amount of catalyst on rate of reduction is complex and has been the subject of considerable study; a review in 1959 contained 126

references to the problem (Fasman and Sokol'skii, 1959). The subject has considerable practical interest inasmuch as the rate of reduction is related to the cost of using a catalyst. Some idea of how the rate of reduction may vary with the amount of catalyst may be gleaned from the rate data of Table II, related to the hydrogenation of nitrobenzene in ethanol over various amounts of 5% palladium-on-carbon (Karpenko, 1962). The catalyst was used at four loading levels and at each level the reduction was carried out in an equipoise shaker, which gives very vigorous agitation, and in a flask stirred by a magnetic stirring bar, which gives relatively poor agitation. Each reduction proceeded at nearly constant rate until the substrate was almost exhausted.

TABLE II

HYDROGENATION OF NITROBENZENE IN ETHANOL[a]

Catalyst (mg)	Metal (mg)	ml H_2/minute		ml H_2/min/mg metal	
		Shaker	Stirrer	Shaker	Stirrer
52	2.6	2.5	2.5	0.96	0.96
105	5.2	43	31	8.2	5.9
210	10.5	118	55	11.2	5.2
420	21	154	55	7.3	2.6

[a] 5% palladium-on-carbon, atmospheric pressure, room temperature.

The complex relationship between the rate and the amount of catalyst may be considered to be the resultant primarily of two factors, inhibition of rate by poisoning and by diffusion, superimposed on a linear relationship between the rate and the amount of catalyst. At low catalyst loading levels where very small amounts of metal are present, the rate is controlled primarily by the amount of poison in the system. A comparison of the rates obtained with 2.6 mg and 5.2 mg palladium suggests that in this system there was enough catalyst poison to deactivate almost all the 2.6 mg metal. The amount of *effective* metal in 5.2 mg is accordingly much greater than double that in 2.6 mg. The rate obtained with 5.2 mg metal is lower in the poorly agitated, stirred system than in the more vigorously agitated system, suggesting that even at these low loading levels the rate is partially controlled by diffusion phenomena in the poorly agitated system. A clearer indication of the effect of diffusion in limiting the rate is seen in the identical rates obtained with 10.5 mg and 21 mg palladium in the stirred system.

Data showing similar trends have been obtained with many other systems, and invariably may be interpreted qualitatively in the same manner. It is important to recognize the pervasive influence that the effects of poisoning and diffusion may have on the rate of reduction in any evaluation of the

effectiveness of a catalyst; failure to do so may lead to gross errors. An estimate of how much catalyst is required to obtain some convenient rate of reduction cannot, with any certainty, be made by measurement at only one catalyst loading level. If the evaluation is made with an amount of catalyst so small that poisons in the system inactivate most of it, the reduction will appear to require much larger amounts of catalyst than, in fact, need actually be used. On the other hand, if too large amounts of catalyst are used (and the amount may be really quite small), the rate will be controlled by diffusion and a large portion of the catalyst may contribute nothing to the rate.

A good illustration of the latter point is found in the hydrogenation of cottonseed oil over 0.5% palladium-on-carbon at 185°C and atmospheric pressure in a 1-gallon stirred autoclave provided with good mechanical agitation. The rate of reduction steadily increased as the concentration of palladium based on oil was increased in increments from 0.0005% to 0.0025%. But beyond 0.0025% no further increase in rate was observed even when 10 times this much catalyst was used. A calculation of the catalyst-functioning rate indicated that with the lowest amount of catalyst tested, 0.0005% palladium, the rate was still in part controlled by hydrogen transport (Zajcew, 1960).

The foregoing description of the factors influencing rate, while correct as far as it goes, is incomplete, and certainly other factors must contribute. Watt and Walling (1955) have established quantitative relationships between catalyst loading and rate. For instance, data showing trends similar to that given in Table II have been obtained for hydrogenation of hexene-1 and allyl alcohol under a variety of conditions. All the results were shown to fit the empirical expression,

$$R_0 = \frac{AWP_{H_2}}{1 + BW}$$

where R_0 is the rate of the zero-order reaction, W is the weight of the catalyst, P_{H_2} is the hydrogen pressure, and A and B are constants. In this work the weights of catalysts were sufficiently large so that poisoning was not observed, and the equation applies only to the limitations on rate by diffusion of hydrogen. A more complex kinetic equation has been derived, based on experimental results from hydrogenation of nitro compounds, which shows the reduction to be first order with respect to hydrogen pressure and fractional order with respect to both substrate and catalyst. As the amount of catalyst is reduced to low levels, the reduction approaches first order with respect to hydrogen pressure, substrate, and catalyst (Yao and Emmett, 1959). For those interested in rationalizing the effect of the amount of catalyst on products obtained, the implications of this equation may provide new avenues of speculation.

Quite apart from a consideration of rate, which is not always constant but at times shows a continuous decline, the amount of catalyst needed is just enough to carry the reduction to completion in a reasonable time. While declining rates are sometimes interpreted as showing a relationship between substrate concentration and rate, the decline is often caused by deactivation of the catalyst. Deactivation can result from a change in the catalyst itself, from some reaction occurring on the catalyst surface, or from some reaction occurring in the bulk of the solution that forms catalyst deactivators. In any event, regardless of the reason for deactivation, it is a fact that better use may sometimes be made of the catalyst if all the catalyst is not in the system during the entire reduction. That is, better use can be made of the catalyst if it is added in several portions rather than all at once (Carothers and Jones, 1925).

EFFECT ON PRODUCT

The products of reduction may vary with the amount of catalyst used in the reaction (DePuy and Story, 1960; Cromwell and Mitsch, 1961; Dobson *et al.*, 1961; Taub *et al.*, 1963), sometimes in a very complex way (Csuros, 1951; Augustine, 1963). As the amount of catalyst in a system is increased, diffusion of hydrogen to the catalyst ultimately becomes rate-limiting and the catalyst becomes hydrogen-poor. Many phenomena connected with the amount of catalyst can be explained in terms of a reversible half-hydrogenated substrate adsorbed on a hydrogen-deficient surface (House *et al.*, 1962; Zajcew, 1960).

Sometimes overhydrogenation may be decreased and selectively improved by use of small amounts of catalyst. For instance, dehydrohalogenation was minimized by use of low catalyst loading levels during reduction of aromatic chloronitro compounds (Rylander *et al.*, 1965) and 1-halobenzoyl-2-iso-propylidenehydrazines (Freifelder *et al.*, 1961), and during debenzylation of aromatic chloro compounds (Adams and Acker, 1952). Improved yields of product may be obtained with high catalyst loading levels when the substrate or products are not stable and undergo other transformations not catalyzed by platinum metals. Very high catalyst loading levels were required to achieve satisfactory reductions of III and IV. Good yields were obtained in

(III)   cis

(IV)   cis
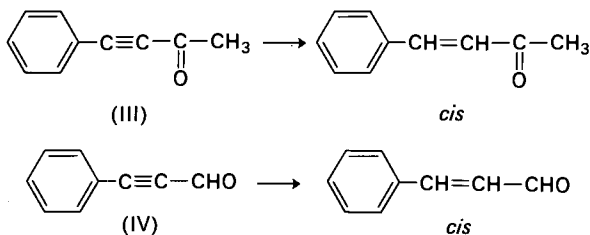
hydrogenation of III with 0.8–1.2 gm 5% palladium-on-calcium carbonate per 2–3 gm substrate, whereas it was necessary to reduce IV over 3.5 times its weight of catalyst to prevent resinification (Schinz, 1955).

III. PRESSURE

Most catalytic hydrogenations over platinum metal catalysts are made at low pressure, 50 psig or less. This fact reflects one of the virtues of platinum metal catalysts. However, as the pressure is raised the rate usually increases, and most reductions can be achieved satisfactorily with appreciably less catalyst at higher pressures. For some reductions, especially those giving a low-cost product, the use of elevated pressures is, on an economic basis, mandatory. There are a few reductions, for example the conversion of carboxylic acids to alcohols, that can be accomplished at present only at high pressure. There are other reductions in which the product changes as the pressure is changed. Pressure is thus one of the important variables bearing on the chemistry and economics of hydrogenation processes.

The effect of pressure on the rate of reduction is not always predictable. For instance, over 5% ruthenium-on-alumina an aqueous glucose solution remained unchanged for 24 hours at 50 psig and room temperature but, at 1000 psig, hydrogenation was complete in a few hours (Karpenko, 1962). On the other hand, the rate of reduction of dimethylnitrosoamine over 10% palladium-on-carbon changed only slightly over this same pressure range; over 5% rhodium-on-carbon a much greater effect of pressure on rate was noted (Smith and Thatcher, 1962). The effect just quoted with palladium is not common and, in general a substantial saving in time and/or catalyst can be made by operating at elevated pressures.

The pressure may also have an important bearing on the yield of product as well as on the rate of reduction. The yield and rate are often related. In all those cases where the substrate, intermediate, or product can interact at substantial rates, or where some intramolecular reaction (for instance, decarboxylation) may occur, it would seem advantageous to reach the final reduction product as soon as possible in order to minimize the time available for unwanted side-reactions. For instance, only by use of high pressure could good yields of 1-phenyl-2-hydrazinopropane be obtained in hydrogenation of phenylacetone hydrazone. Optimum conditions involved the use of platinum oxide or platinum-on-a carrier in alcoholic acetic acid at 2000 psig. Coupling or hydrogenolysis products predominated when, with a variety of solvents and catalysts, the reduction proceeded slowly (Biel et al., 1959).

In the contrary situation where the desired product is derived through a side-reaction, it may be desirable to operate at subatmospheric pressure so as to reduce the rate of hydrogenation relative to the rate of the alternative

reaction. A case in point is the reduction of nitrobenzene over platinum-on-carbon in acid solution to *p*-aminophenol (Spiegler, 1956). Yields of *p*-amino-phenol approaching 100% are obtained when the hydrogen partial pressure is 100 mm mercury; the yields are only about 40% when the pressure is 500 mm.

In those reductions where both major and minor products are derived by hydrogenation, it is difficult to assess a priori how a change in pressure will alter the product distribution. The direction of change may depend both on the pressure range examined and on the substrate. For instance, in hydrogenation of 4-*t*-butyl-1-methylcyclohexene over platinum oxide in acetic acid, the ratio of *cis* to *trans* isomers in the resulting cyclohexane increased with increased pressure over a wide pressure range, but the ratio steadily decreased when isomeric 4-*t*-butyl-1-methylenecyclohexane was the substrate (Siegel and Dmuchovsky, 1962). The effect of pressure on the proportion of *cis-trans* isomers obtained in reduction of the isomeric xylenes and of *t*-butyltoluene depends both on the pressure range examined and on the substrate. The proportion of *cis* isomer increased for each substrate with an increase in the pressure of hydrogen for pressures over 2 atm. At lower pressures the ratios changed in a manner characteristic of each substrate (Siegel *et al.*, 1962).

Reduction of ethyl *p*-hydroxybenzoate at 43 psig over palladium-on-strontium carbonate gave 2.7 parts of the ring-saturated product, ethyl 4-hydroxycyclohexanecarboxylate, and 1.0 part of the hydrogenolysis product, ethyl cyclohexanecarboxylate; reduction at high pressure gave a quantitative yield of the 4-hydroxy ester. High pressure evidently favors hydrogenation relative to hydrogenolysis in this reduction (Levin and Pendergrass, 1947).

IV. AGITATION

Adequate agitation in catalytic hydrogenation is important, especially in industrial processes where economy becomes a decisive issue, for the rate of reduction is related to and may be limited by the rate hydrogen is supplied to the catalyst surface. Poor agitation in laboratory work usually carries no untoward consequences, except perhaps a faulty appraisal of the catalyst activity, but in large-scale processing failure to provide sufficient agitation can be and has been very costly. This deficiency is not always recognized as such, because it may appear that adequate agitation has been provided when in fact it has not. The problem of inadequate mixing some-times disappears when a process is scaled-up; reductions frequently proceed better in large equipment than in small. Inadequate agitation may be deliber-ately employed as a convenient and effective way of moderating highly exothermic hydrogenations.

Poor mixing may have an adverse effect on catalyst life as well as on rate. The effect on life is not well documented, but nonetheless the problem seems worthy of consideration. It has been observed, for instance, that in certain but not all reductions the rate showed a decline when the reduction was continued after the agitation had been stopped for a time (Hasbrouck, 1966). Other workers have also noted catalyst damage when a hydrogenation was interrupted (Martin and Robinson, 1943). The adverse effect on catalyst life of inadequate mixing may be expected to increase as the conditions become more vigorous, inasmuch as an unnecessarily lengthy reduction allows more time for formation of thermally induced catalyst deactivators.

Catalyst deactivation may arise on hydrogen-deficient catalysts through condensation and polymerization of half-hydrogenated products. Failure to reduce hydroquinone in water over rhodium-on-carbon granules in fixed-bed processing at atmospheric pressure was attributed to this cause. In a short time so much insoluble yellow material had formed on the catalyst that it could be scraped off manually. On the other hand, this reduction proceeds smoothly to cyclohexanediol over powdered rhodium-on-carbon in a vigorously stirred system (Rylander and Wisla, 1957). Hydrogenation of 3-cyclohexene-1-carboxaldehyde to cyclohexanecarboxyaldehyde was unsuccessful in a rocker bomb, but proceeded smoothly with the better agitation of a stirred autoclave (Hennis and Trapp, 1961).

Sometimes relatively small increases in agitation cause disproportionately large increases in rate of reduction. For instance, in hydrogenation of the δ-lactone of d-gluconic acid over platinum oxide, carried out in a Burgess–Parr apparatus, the time necessary for 50% reduction was decreased from 20 hours to 30 minutes when the rate of shaking was increased from 120 to 350 cycles per minute (Glattfeld and Schimpff, 1935).

EFFECT ON PRODUCT

The product as well as the rate of hydrogenation may be influenced by the amount of agitation. For instance, in hydrogenation of fatty oils both the selectivity (preferential hydrogenation of multiple unsaturation) and the percentage of *trans* isomers formed depend on the agitation. The *trans* content of a partially hydrogenated oil was 38% when the reduction was stirred at 800 rpm, but at 290 rpm rose to 55%. These effects were interpreted in terms of varying hydrogen supply at the catalyst surface (Zajcew, 1960). Conversely, in the following example increased agitation led to increased *trans* isomer content. The *cis-trans* isomer ratio obtained in partial hydrogenation of 1-chloro-4,7,10,13-nonadecatetrayne to the tetraene depended on the catalyst activity, temperature, and rate of hydrogenation. *Trans* isomers were minimized by maintaining the rate of hydrogen

absorption in a magnetically stirred reactor at 5–6 ml H_2/min; higher rates led to increasing proportions of *trans* double-bonded products (Ege *et al.*, 1961).

Although the effect of agitation on the products of hydrogenation may be difficult to predict, it would seem that this effect, once ascertained, should provide a convenient guide for the effects of changing other variables, provided all changes in product are brought about by varying hydrogen supply at the catalyst surface. For instance, if it is ascertained that the relative amount of a product is increased by increasing the agitation (i.e., by making the catalyst hydrogen-rich), then it might be assumed that other changes that will make the catalyst more hydrogen-rich will also increase the product. Following this reasoning, the product would be increased by increasing the pressure, lowering the temperature, and using a partially deactivated catalyst. The product would also be favored by using less catalyst so that the available hydrogen is divided among fewer particles.

V. MODE OF ADDITION

Usually in a catalytic hydrogenation the substrate with or without solvent is present throughout the entire reduction. Often the catalyst in solvent is prereduced by shaking with hydrogen, the substrate added all at once, and the reduction begun. However, sometimes superior yields of product can be obtained by adding the substrate gradually instead of having it all initially present. For example, 1,2-epoxyphenylethane can be reduced with Raney nickel or ruthenium-on-alumina to cyclohexylethyl alcohol. By addition of 1000 gm substrate in ethanol over a 3-hour period at 140°C and 100 atm a 75.5% yield of cyclohexylethyl alcohol is obtained. Under identical conditions the yield is only 45% if the substrate is introduced all at once (Bo and Perras, 1963). Another application of a dropwise addition technique is the preparation of 7-amino-6-ethyl-1-ketomerimine (VI). The substrate (V) dissolved in acetic acid was added dropwise over a 2-hour period to an unusual palladium-on-carbon catalyst in hydrochloric acid. The catalyst was prepared *in situ* by hydrogenating a mixture of activated charcoal and an aqueous acid palladium chloride solution at $-40°C$ (Gadekar *et al.*, 1961).
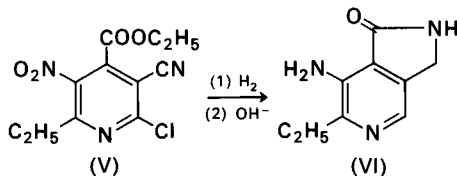
Dropwise addition might be expected to be a generally useful technique when the catalyst is deactivated by overly strong adsorption of the substrate

(Breitner *et al.*, 1959a). The technique might also prove useful when the substrate is not sufficiently miscible with the solvent, as in reduction of nitrobenzene to *p*-hydroxyaniline in sulfuric acid. By adding the substrate at such a rate that no appreciable amount of it remained undissolved, a considerably increased rate was achieved (Spiegler, 1956). Dropwise addition of the substrate is also generally useful when the hydrogenation reaction competes with other types of reaction. The improved yields of cyclohexyl-ethyl alcohol cited above can be attributed to diminished chance of inter-action of the substrate with itself or with the solvent before undergoing hydrogenation.

VI. SOLVENTS

A solvent* is used in most liquid phase hydrogenations with advantage; solids, of course, cannot be hydrogenated otherwise, unless melted (Winstrom and Snider, 1964). Normally liquid substrates are reduced more easily, and handling of small quantities of substrates is facilitated; in large reductions, the solvent is useful for controlling the temperature rise resulting from highly exothermic reactions. But the solvent is much more than an inert medium in which to dissolve the substrate; the rate and sometimes the course of reduction depend critically on the solvent used.

Most liquid materials that are stable under hydrogenation conditions and do not inactivate the catalyst can be used as solvents. Mineral and carboxylic acids, esters, ethers, amines, amides, anhydrides, sulfoxides, sulfones, hydrocarbons, and water have all been used as solvents in hydrogenation reactions. Acetic acid, methanol, and ethanol are the most commonly used. Dioxane may react *explosively* with hydrogen and Raney nickel above 200°C (Mozingo, 1955). Whether dioxane also undergoes explosive decomposition over platinum metal catalysts at elevated temperatures does not seem to have been reported.

In the following sections, some general influences of solvent on hydrogenation are considered. Many specific references to solvent effects are given throughout the sections on hydrogenation of various functional groups.

A. Effect on Rate

Solvents may cause extreme variations in the rate of hydrogenation. Often the solvent has more influence on the rate than the catalytic metal or

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* The term "solvent" is used with broad implications. It may actually be a reactant (e.g., acetic anhydride solvent in reduction of nitro compounds). It may be the product itself (e.g., cyclohexanol as a solvent in reduction of phenol). We have extended the definition, for lack of a better term, to include cases where the substrate is essentially insoluble in the "solvent" (e.g., water in reduction of olefins over ruthenium).

carrier. Very few generalities can be given as guides in choosing a solvent, where the criterion for usefulness is a rapid rate of reduction; a conclusion reached four decades ago, that the effect of solvent on rate seems to some extent to be specific for each system, still stands (Carothers and Adams, 1923). Various efforts to correlate the rate with physical properties of the solvent have not been too successful (Maxted and Stone, 1938; Sokol'skii, 1964). Considering that the rate of hydrogenation is influenced by such factors involving the solvent as tendency of the catalyst to agglomerate, inhibitors initially in the solvent or formed in the reduction, substrate solubility (Zhanalinova and Sokol'skii, 1958), competition of solvent, substrate, and product for catalytic sites, interaction of solvent and substrate, and hydrogen solubility,* it is unlikely that general correlations between rate and solvent will be forthcoming. Often the rate of reduction in solvents constituting a homologous series decreases appreciably as the series is ascended, but even this generality is subject to exception (Klemm and Mann, 1964). Hydrogenations over ruthenium catalysts at low pressures are most rapidly carried out in water, even though the substrate may be water-insoluble (Berkowitz and Rylander, 1959).

1. Acidic Media

An acidic solvent is frequently useful in nullifying the inhibiting effect of amine substrates (Devereux et al., 1957) or of amines formed in reduction of oximes (Breitner et al., 1959b), nitro compounds (Oelschläger, 1956), nitriles (Rosenmund and Pfannkuch, 1923), or pyridines (Freifelder, 1963). All acidic media are not necessarily equivalent; N-methylpyrrole was reduced easily over platinum oxide in absolute alcohol containing one equivalent of hydrochloric acid (Craig and Hixon, 1931), but the reduction was very sluggish in glacial acetic acid (Wibaut, 1925).

Tetrasubstituted carbon–carbon double bonds may be reduced over platinum oxide in acetic acid but not in neutral solvent. This rate difference has been used as a diagnostic test for presence of tetrasubstituted bonds (Kealy and Benson, 1961).

2. Agglomeration

Occasionally catalysts show a marked tendency to agglomerate. For instance, reduction of 2-benzoylpyridine to phenyl-2-piperidylcarbinol over platinum oxide required an excess of hydrochloric acid to avoid catalyst deactivation through agglomeration. A solution of the hydrochloride of

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* Battino and Clever (1966) have reviewed solubility data for hydrogen and other gases in various solvents.

this pyridine in water appeared cloudy due to hydrolysis; attempted hydrogenation caused clumping of the catalyst and no hydrogen was absorbed. A series of experiments established the optimum amount of acid to be 100–125% excess hydrochloric acid over that necessary to form the hydrochloride in a 7% solution of the pyridine in water (Crook and McElvain, 1930). Agglomeration of a catalyst always affects the rate adversely and, if severe, may spell failure for the reduction. Agglomeration may frequently be overcome by changing the pH of the medium, or by changing the solvent, the solvent-to-substrate ratio, or the catalyst carrier.

B. EFFECT ON THE PRODUCT

The effect of solvent on the products of reduction is usually more predictable than the effect on rate, for, whereas the rate depends on all the vagaries inherent in catalytic phenomena, the products are often but not always predictable from the better established rationale of organic chemistry.

1. *Interaction between Solvent and Substrate or Product*

Solvents may alter a reduction through interaction with either the substrate or product. Esters may be formed during catalytic hydrogenation of carboxylic acids in alcohol solvent. Ester formation occurred during hydrogenation of benzoic acid and cinnamic acid in ethanol; the esterification was catalyzed by traces of hydrogen chloride still bound to the catalyst (Kindler and Helling, 1957). Extensive ester exchange occurred during reduction of a series of *p*-nitrobenzoic acid esters in ethanol over either Raney nickel or palladium-on-carbon; this difficulty was circumvented by using benzene as a solvent (Kaye and Roberts, 1951.* Under vigorous conditions alcoholysis of amides may occur (Wojcik and Adkins, 1934). Reduction of alcohols in an acid solvent may also afford esters. Hydrogenation of cholesterol in acetic acid over platinum oxide resulted in formation of a considerable amount of cholestanyl acetate, necessitating hydrolysis of the entire product to obtain pure cholestanol. The reduction is also frequently sluggish. Both these difficulties were obviated by use of ethyl acetate containing a promoter (Hershberg *et al.*, 1951). Another modification in hydrogenation of cholesterol was the use of cyclohexane-acetic acid solvent, which prevented catalyst deactivation through crystallization of the hydrogenation products (Nace, 1951).

Alcohol solvents and aldehydes are apt to interact during catalytic hydrogenation to afford acetals. Very small amounts of ferrous chloride, in iron-

* In other work, ester exchange occurred over platinum oxide but not over platinum oxide-on-silicic acid (Ackman and Burgher, 1964).

promoted platinum oxide catalysts, caused heptaldehyde in 95% ethanol to interact with liberation of heat, and the reductions ceased at 80% of completion. The use of 70% ethanol diminished acetal formation and reductions were 90–95% complete (Carothers and Adams, 1923). Acetal formation occurred also when benzaldehyde was reduced in methanol. The degree of completion of the hydrogenation varied with the methanol used; with technical methanol the reaction stopped at 70% of completion, with perfectly neutral absolute methanol at 94% of completion, and with methanol distilled from sodium at 100% of completion (Carothers and Adams, 1924). Alcohol proved to be a useless solvent for hydrogenation of a pivalaldehyde over platinum oxide, whereas acetic acid was excellent (Cheney, 1951).

Hydrogenation of 3-oxo-4-ene steroids in ethanol over palladium hydroxide afforded large amounts of 3-ethoxy compounds together with small amounts of saturated alcohol. This reaction was suppressed strongly by addition of either alkali or hydrochloric acid. The ethoxy compounds may have arisen from interaction of the solvent with either the saturated or unsaturated ketones; examination of the products at intermediate stages of hydrogenation provided evidence for both courses (Nishimura et al., 1966).

Alcohols, under vigorous conditions in the presence of amines, undergo reductive alkylation (Adkins and Cramer, 1930), a difficulty obviated by use of ruthenium catalysts (Freifelder and Stone, 1961).

   a. Condensations and Rearrangements. The solvent may catalyze condensation of the substrate. Catalytic hydrogenation of cholestanone over platinum in di-n-butyl ether containing a small amount of concentrated aqueous hydrobromic acid affords epicholestanol as the major product together with a small amount of cholestanol (Vavon and Jakubowicz, 1933; Ruzicka et al., 1934) but, if an acetic acid solution of hydrogen bromide is used instead of a concentrated aqueous solution, an aldol coupling product of cholestanone is obtained in 40% yield (Corey and Young, 1955). Another example of the solvent influencing the product through its condensing action is the reduction over palladium of p-nitroanisole in liquid hydrogen fluoride containing phenol; 4-hydroxy-4-methoxydiphenylamine was obtained in 66% yield (Weinmayr, 1956).

The solvent may cause rearrangement of a partially hydrogenated intermediate. Nitrobenzene hydrogenated in sulfuric acid affords p-aminophenol (Spiegler, 1956) and, in hydrogen fluoride, p-fluoroaniline (Fidler et al., 1961).

   b. Acylations Acid anhydrides are used as solvents in some reductions with the intention of obtaining an acylated product. When a nitro compound is reduced in acetic anhydride, the acetyl derivative is obtained directly from the reaction mixture. Reduction of ethyl 2-methyl-5-nitronicotinate in acetic anhydride–acetic acid over platinum oxide gave, as expected, ethyl

5-acetylamino-2-methylnicotinate, whereas reduction in ethanol gave a mixture of the free amine and partially reduced products (Fanta, 1953). Acetylated primary amines are obtained by reduction of nitriles in acetic anhydride. Acetylation effectively removes the primary amine as it is formed and prevents coupling reactions (Carothers and Jones, 1925).

2. Stabilization of Products

Sensitive compounds may be readily obtained by catalytic hydrogenations if the solvent is chosen with care and in accordance with the chemical properties of the product. Three examples below illustrate the point. The amine obtained by reduction of optically active 2-nitrooctane over platinum oxide in ethanol was 96% racemized, whereas in acetic acid solvent at least 72% stereospecificity was preserved. Acetic acid neutralized the basic amine as it was formed and prevented racemization of the unchanged nitrooctane by the free amine (Kornblum and Fishbein, 1955). Reductive cleavage of acetylated benzylglycosides, which permitted isolation of unmutarotated 1-hydroxy acetylated aldoses, was achieved by palladium and hydrogen with absolute ether as a solvent; acetic acid or ethyl alcohol solvent caused extensive mutarotation (Ballou et al., 1951). A buffered solution was used advantageously in hydrogenolysis of the carbobenzoxy groups of O,N-dicarbobenzoxy-des-N-methylerythromycin to protect the acid-sensitive hydrogenolysis product against acid-catalyzed hydrolysis or alcoholysis. Use of a sodium acetate–acetic acid-buffered solution protected the acid-sensitive product against trace amounts of hydrogen chloride arising through hydrogenolysis of trace amounts of contaminating carbobenzoxy chloride (Flynn et al., 1955).

3. Neutral and Charged Substrates

In many reductions the solvent may influence the products by changing the charge on the species actually undergoing hydrogenation. Extensive decarboxylation accompanies hydrogenation of nicotinic acid in neutral solution, whereas neither the hydrochloride or sodium salt undergoes appreciable decarboxylation (Freifelder and Stone, 1961). Poor results were obtained in attempts to reduce chlorocyanopyridine to aminomethylpyridine in either acidic or strongly basic media, whereas in neutral or slightly alkaline media one mole of hydrogen was rapidly absorbed followed by two more after the solution was acidified (Godar and Mariella, 1960). Formation of a stable, protonated, ionic intermediate was postulated to explain failure to obtain 5,6,7-trimethylindole from 3,4,5-trimethyl-2,β-dinitrostyrene on reduction in a methanol–acetic acid–ethyl acetate solution in the presence of 10% palladium-on-carbon. The reduction stopped at 60% of the theoretical

absorption and none of the indole could be isolated. However, when the hydrogenation was carried out with ethyl acetate–methanol as a solvent, hydrogen absorption was rapid and complete and the indole was isolated in 50% yield (Benington et al., 1960).

Protonation of a substrate may change either or both the conformation of the reacting species and the mode of adsorption on the catalyst. Reduction of the azabicyclic ketones (VII, VIII, and IX) varied with the ring size and with the solvent, as indicated. The authors suggested that the effect of solvent is indicative of at least partial protonation on nitrogen in acetic acid, or alternatively, that the effect could be interpreted as evidence for an interaction between the nitrogen atom and the catalyst surface in neutral media (House et al., 1963). Similarly, the relative amounts of epimeric hydroxyquinolizidines derived by hydrogenation of 1-, 2-, or 3-ketoquinolizidine were found to vary widely with neutral and acidic solvents and also with catalyst (see page 285) (Rader et al., 1964).

(VII)	n = 1	HOAc		81%	19%
	n = 1	i-PrOH		98%	2%
(VIII)	n = 2	HOAc		4%	96%
	n = 2	i-PrOH		38%	62%
(IX)	n = 3	HOAc		<1%	>99%
	n = 3	i-PrOH		1%	99%

4. Strong Acids

Kindler and co-workers, in a series of papers under the general heading of the importance of molecular compounds in catalytic hydrogenation, developed the advantageous use of strong acid in solvents. Reduction of β-nitrostyrene in acetic acid–sulfuric acid is rapid and affords phenylethylamine in 90% yield; in the absence of sulfuric acid, reduction is slow and the yield of amine low (Kindler et al., 1934). Reduction of m-nitroacylbenzenes to m-alkylamines proceeded smoothly over palladium in acetic acid–sulfuric acid monohydrate. In the absence of sulfuric acid, no trace of the aniline was found (Oelschläger, 1956). Hydrogenation of esters of mandelonitrile over palladium chloride-on-carbon affords phenylethylamine in high yield in methanol containing sulfuric acid or hydrochloric acid, but when the strong acid is omitted the principal product is benzyl cyanide (Kindler and Schrader, 1949). Hydrogenation of O-acetylmandelic esters in the presence of sulfuric

acid and palladium gives in addition to phenylacetic esters considerable quantities of ring-saturated esters; ring saturation may be prevented by addition of hydrogen bromide or zinc chloride. The effect of sulfuric acid and perchloric acid on product distribution in hydrogenation of ethyl benzoylmalonate and ethyl benzoylacetate (Kindler and Blaas, 1943) and mandelic acid and its esters (Kindler and Dschi-yin-Kwok, 1943) has been discussed. Sulfuric acid, zinc chloride, and boron trifluoride may all be used as activators in synthesis of β-arylalkylamines over palladium-on-barium sulfate, but perchloric acid is more effective (Rosenmund et al., 1942). Use of sulfuric acid-water rather than sulfuric acid has been recommended to prevent catalyst poisoning by hydrogen sulfide (Kindler et al., 1948). Other papers describe the advantageous use of sulfuric acid in synthesis of amines (Kindler et al., 1935) and in promoting hydrogenolysis (Kindler and Peschke, 1935). Large amounts of perchloric acid promote reduction of aromatic rings. For example, cyclohexylethylamine was obtained in 72% yield from reduction over palladium of β-nitrostyrene in a solvent of 13% perchloric acid (70% solution) and 87% acetic acid (Kindler et al., 1948).

Strong acids may influence the product through interaction with an intermediate. Reduction of ethyl β-isatylidene-β-hydroxypropionate over palladium-on-carbon in ethanol stopped spontaneously after absorption of one mole to give ethyl β-hydroxy-β-oxindole-3-propionate. However, when reduction was carried out in glacial acetic acid containing a small amount of sulfuric acid, two moles of hydrogen were absorbed, to afford ethyl oxindole-3-propionate. The acetic acid–sulfuric acid solution was shown to dehydrate readily the intermediate hydroxy compound to give ethyl β-isatylidenepropionate, a compound easily reduced to ethyl oxindole-3-propionate (Julian and Printy, 1953).

5. Solvent-to-Substrate Ratio

In general the ratio of solvent to substrate in a hydrogenation may be varied widely with little effect on the reduction. However, in some reductions the rate (Glattfeld and Schimpff, 1935) and, of more interest, the product change with the substrate concentration (Huffman and Browder, 1964; Londergan et al., 1953; Skinner, 1966). Selective hydrogenation of multiple unsaturation in a steroid was achieved satisfactorily only with strict adherence to a weight-volume ratio, e.g., 4.54 gm substrate in 105 ml 95% methanol (Kurath et al., 1963).

6. Competition, Complex Formation, and Diffusion Control

The solvent, beyond actually interacting with the substrate or intermediate in a clearly definable way, may also influence the course of reduction in

more subtle ways, the details of which usually can only be inferred. Three of these ways may be conveniently called competition, complex formation, and diffusion control.

a. Competition. The results obtained in reduction of cholestenone and testosterone suggest that the product is controlled through direct competition of substrate and solvent for catalyst sites. The proportions of α- and β-isomers formed on reduction of these steroids over palladium-on-carbon varied widely with the solvent. The ratio of β- to α-isomer obtained in reduction of cholestenone varied from 10 in alkaline methanol to 2.4 in hexane. The authors suggested that the correlation between isomer ratio and solvent properties is to be found in the electron-donor capacity of the solvent (McQuillin *et al.*, 1963). The solvent was thought to more or less control by competition the extent to which the carbonyl function of the substrate was adsorbed on the catalyst. In the alcohol series—methanol, ethanol, isopropanol, and *t*-butanol, the isomer ratio fell from 8 in the first to 2.1 in the last, paralleling the progressive masking of the hydroxyl function, which rendered the heavier alcohol less prone to adsorb competitively on the catalyst. The effect of solvent on the stereochemistry of hydrogenation of 3-oxo-4-ene steroids over unsupported palladium has also been examined (Nishimura *et al.*, 1966).

b. Complex Formation. The concept of complex formation was used to explain the different products arising from hydrogenation of benzoyl-carbinyl acetate. Catalytic reduction of this substrate in the presence of palladium ceased after absorption of one mole of hydrogen to give $C_6H_5CH(OH)CH_2OAc$ when the solvent was cyclohexane, benzene, or toluene, but, when an oxygenated solvent (methanol, dioxane, ethyl acetate, or acetic acid) was used, two moles of hydrogen were absorbed to give $C_6H_5CH_2CH_2OAc$ in 70–80% yield. It was assumed, with supporting evidence, that oxygen-containing solvents coordinated with the hydroxyl group formed on absorption of one mole and facilitated further reduction (Kindler and Blaas, 1944). A similar explanation accounts for the effect of solvent on the extent of dehydrohalogenation occurring in selective reduction of allylhalophenols to propylhalophenols over palladium. Hydrogenation of 4-chloro- or 4-bromo-2-allylphenol in 80% aqueous ethanol, absolute ethanol, isopropanol, butanol, acetic acid, or dioxane resulted in appreciable dehydrohalogenation, but in benzene or cyclohexane no detectable halogen was eliminated (Kindler *et al.*, 1953).

c. Diffusion Control. Finally, the solvent may in part determine the composition of the product by influencing the availability of hydrogen at the catalyst surface (Yao and Emmett, 1959). Both selectivity and *trans* isomer formation in hydrogenation of natural fats have been linked to hydrogen

availability at the catalyst surface, and the effect of solvent on product composition can probably be correctly attributed to the role of the solvent in facilitating hydrogen transport (Zajcew, 1960).

REFERENCES

Ackman, R. G., and Burgher, R. D., *J. Lipid Res.*, 5(1), 130 (1964).
Adams, R., and Acker, D. S., *J. Am. Chem. Soc.* 74, 3029 (1952).
Adkins, H., and Cramer, H. I., *J. Am. Chem. Soc.* 52, 4349 (1930).
Augustine, R. L., *J. Org. Chem.* 28, 152 (1963).
Ballou, C. E., Roseman, S., and Link, K. P., *J. Am. Chem. Soc.* 73, 1140 (1951).
Battino, R., and Clever, H. L., *Chem. Rev.* 66, 395 (1966).
Benington, F., Morin, R. D., and Clark, L. C., Jr., *J. Org. Chem.* 25, 1542 (1960).
Berkowitz, L. M., and Rylander, P. N., *J. Org. Chem.* 24, 708 (1959).
Biel, J. H., Drukker, A. E., Mitchell, T. F., Sprengeler, E. P., Nahfer, P. A., Conway, A. C., and Horita, A., *J. Am. Chem. Soc.* 81, 2805 (1959).
Bo, G., and Perras, P., U.S. Patent 3,109,863, Nov. 5, 1963.
Breitner, E., Roginski, E., and Rylander, P. N., *J. Org. Chem.* 24, 1855 (1959a).
Breitner, E., Roginski, E., and Rylander, P. N., *J. Chem. Soc.* p. 2918 (1959b).
Carothers, W. H., and Adams, R., *J. Am. Chem. Soc.* 45, 1071 (1923).
Carothers, W. H., and Adams, R., *J. Am. Chem. Soc.* 46, 1675 (1924).
Carothers, W. H., and Jones, G. A., *J. Am. Chem. Soc.* 47, 3051 (1925).
Cheney, L. C., *J. Am. Chem. Soc.* 73, 685 (1951).
Cocker, W., Shannon, P. V. R., and Staniland, P. A., *J. Chem. Soc.* (C), p. 41 (1966).
Corey, E. J., and Young, R. L., *J. Am. Chem. Soc.* 77, 1672 (1955).
Craig, L. C., and Hixon, R. M., *J. Am. Chem. Soc.* 53, 187 (1931).
Cromwell, N. H., and Mitsch, R. A., *J. Org. Chem.* 26, 3812 (1961).
Crook, K. E., and McElvain, S. M., *J. Am. Chem. Soc.* 52, 4006 (1930).
Csuros, Z., *Research (London)* 4, 52 (1951).
DeGraw, J. I., Ross, L. O., Goodman, L., and Baker, B. R., *J. Org. Chem.* 26, 1933 (1961).
DePuy, C. H., and Story, P. R., *J. Am. Chem. Soc.* 82, 627 (1960).
Devereux, J. M., Payne, K. R., and Peeling, E. R. A., *J. Chem. Soc.* p. 2845 (1957).
Dobson, N. A., Eglinton, G., Kirshnamurti, M., Raphael, R. A., and Willis, R. G., *Tetrahedron* 16, 16 (1961).
Ege, S. N., Wolovsky, R., and Gensler, W. J., *J. Am. Chem. Soc.* 83, 3080 (1961).
Fanta, P. E., *J. Am. Chem. Soc.* 75, 737 (1953).
Fasman, A. B., and Sokol'skii, D. V., *Tr. Inst. Khim. Akad. Nauk Kaz. SSR* 5, 114 (1959).
Fidler, D. A., Logan, J. S., and Boudakian, M. M., *J. Org. Chem.* 26, 4014 (1961).
Flynn, E. H., Murphy, H. W., and McMahon, R. E., *J. Am. Chem. Soc.* 77, 3104 (1955).
Freifelder, M., *Advan. Catalysis* 14, 203 (1963).
Freifelder, M., and Stone, G. R., *J. Org. Chem.* 26, 3805 (1961a).
Freifelder, M., Martin, W. B., Stone, G. R., and Coffin, E. L., *J. Org. Chem.* 26, 383 (1961).
Gadekar, S. M., Frederick, J. L., Semb, J., and Vaughan, J. R., Jr., *J. Org. Chem.* 26, 468 (1961).
Glattfeld, J. W. E., and Schimpff, G. W., *J. Am. Chem. Soc.* 57, 2204 (1935).
Godar, E. M., and Mariella, R. P., *J. Org. Chem.* 25, 557 (1960).
Hasbrouck, L., Unpublished observations, Engelhard Ind., 1966.
Hennis, H. E., and Trapp, W. B., *J. Org. Chem.* 26, 4678 (1961).
Hershberg, E. B., Oliveto, E., Rubin, M., Staeudle, H., and Kuhlen, L., *J. Am. Chem. Soc.* 73, 1144 (1951).

Himelstein, N., Unpublished observations. Engelhard Ind., 1964.

House, H. O., Carlson, R. G., Müller, H., Noltes, A. W., and Slater, C. D., *J. Am. Chem. Soc.* **84**, 2614 (1962).

House, H. O., Müller, H. C., Pitt, C. G., and Wickham, P. P. *J. Org. Chem.* **28**, 2407 (1963).

Huffman, J. W., and Browder, L. E., *J. Org. Chem.* **29**, 2598 (1964).

Julian, P. L., and Printy, H. C., *J. Am. Chem. Soc.* **75**, 5301 (1953).

Karpenko, I., Unpublished observations, Engelhard Ind., 1962.

Kaye, I. A. and Roberts, I. M., *J. Am. Chem. Soc.*, **73**, 4762 (1951).

Kealy, T. J., and Benson, R. E., *J. Org. Chem.* **26**, 3126 (1961).

Kindler, K., and Blaas, L., *Chem. Ber.* **76B**, 1211 (1943).

Kindler, K., and Blaas, L., *Chem. Ber.* **77B**, 585 (1944).

Kindler, K., and Dschi-yin-Kwok, *Ann. Chem. Liebigs* **554**, 9 (1943).

Kindler, K., and Helling, H. G., *Chem. Ber.* **90**, 750 (1957).

Kindler, K., and Peschke, W., *Ann. Chem. Liebigs* **519**, 291 (1935).

Kindler, K., and Schrader, K., *Ann. Chem. Liebigs* **564**, 49 (1949).

Kindler, K., Brandt, E., and Gehlaar, E., *Ann. Chem. Liebigs* **511**, 209 (1934).

Kindler, K., Peschke, W., and Brandt, E., *Chem. Ber.* **68B**, 2241 (1935).

Kindler, K., Hedemann, B., and Schärfe, E., *Ann. Chem. Liebigs* **560**, 215 (1948).

Kindler, K., Oelschläger, H., and Henrich, P., *Chem. Ber.* **86**, 167 (1953).

Klemm, L. H., and Mann, R., *J. Org. Chem.* **29**, 900 (1964).

Kornblum, N., and Fishbein, L., *J. Am. Chem. Soc.* **77**, 6266 (1955).

Kurath, P., Cole, W., Tadanier, J., Freifelder, M., Stone, G. R., and Schuber, E. V., *J. Org. Chem.* **28**, 2189 (1963).

Levin, R. H., and Pendergrass, J. H., *J. Am. Chem. Soc.* **66**, 2436 (1947).

Londergan, T. E., Hause, N. L., and Schmitz, W. R., *J. Am. Chem. Soc.* **75**, 4456 (1953).

McQuillin, F. J., Ord, W. O., and Simpson, P. L., *J. Chem. Soc.* p. 5996 (1963).

Martin, R. H., and Robinson, R., *J. Chem. Soc.* p. 491 (1943).

Maxted, E. B., and Stone, V., *J. Chem. Soc.* p. 454 (1938).

Meister, H., and Franke, W., U.S. Patent 2,886,596, May 12, 1959.

Mozingo, R., *in* "Organic Syntheses," (Horning, E. G., ed.). Collected Vol. III, p. 181. Wiley, New York, 1955.

Nace, H. R., *J. Am. Chem. Soc.* **73**, 2379 (1951).

Nickon, A., and Bagli, J. F., *J. Am. Chem. Soc.* **83**, 1498 (1961).

Nishimura, S., Shimahara, M., and Shiota, M., *J. Org. Chem.* **31**, 2394 (1966).

Oelschläger, H., *Chem. Ber.* **89**, 2025 (1956).

Pierce, J. S., and Parks, C., *J. Am. Chem. Soc.* **51**, 3384 (1929).

Rader, C. P., Wicks, G. E., Jr., Young, R. L., Jr., and Aaron, H. S., *J. Org. Chem.* **29**, 2252 (1964).

Riesz, C. H., and Weber, H. S., *J. Am. Oil Chemists' Soc.* **41** (6), 400 (1964).

Rosenmund, K. W., and Pfannkuch, E., *Chem. Ber.* **56B**, 2258 (1923).

Rosenmund, K. W., Korg, W. E., and Marus, F. K., *Chem. Ber.* **75B**, 1850 (1942).

Ruzicka, L., Brunnger, H., Eichenberger, E., and Meyers, J., *Helv. Chim. Acta* **17**, 1407 (1934).

Rylander, P. N., and Steele, D. R., *Engelhard Ind. Tech. Bull.* **3**, 91 (1962).

Rylander, P. N., and Wisla, I., Unpublished observations, Engelhard Ind., 1957.

Rylander, P. N., Kilroy, M., and Coven, V., *Engelhard Ind. Tech. Bull.* **6**, 11 (1965).

Schinz, H., *Kosmetik-Parfum-Drogen Rundschau* p. 1 (1955).

Siegel, S., and Dmuchovsky, B., *J. Am. Chem. Soc.* **84**, 3132 (1962).

Siegel, S., Smith, G. V., Dmuchovsky, B., Dubbell, D., and Halpern, W., *J. Am. Chem. Soc.* **84**, 3136 (1962).

Skinner, J. R., U.S. Patent 3,260,759, July 12, 1966.

Smith, G. W., and Thatcher, D. N., *Ind. Eng. Chem. Prod. Res. Develop.* **1** (2), 117 (1962).

Smith, H. A., and Stump, B. L., *J. Am. Chem. Soc.* **83**, 2739 (1961).

Sokol'skii, D. V., "Hydrogenation in Solutions" Davey, New York, 1964.

Spiegler, L., U.S. Patent 2,765,342, Oct. 2, 1956.

Taub, D., Kuo, C. H., Slates, H. L., and Wendler, N. J., *Tetrahedron* **19**, 1 (1963).

Tsybina, N., and Mokhova, V. S., *Zh. Prikl. Khim.* **37** (2), 441 (1964).

Tuley, W. F., and Adams, R., *J. Am. Chem. Soc.* **47**, 3061 (1925).

Vavon, G., and Jakubowicz, B., *Bull. Soc. Chim. France* **53**, 581 (1933).

Walker, G. N., *J. Org. Chem.* **23**, 133 (1958).

Walker, G. N., *J. Org. Chem.* **27**, 2966 (1962).

Watt, G. W., and Walling, M. T., Jr., *J. Phys. Chem.* **59**, 7 (1955).

Weinmayr, V., *J. Am. Chem. Soc.* **77**, 1762 (1956).

Wibaut, J. P., *Rec. Trav. Chim.* **44**, 1101 (1925).

Winstrom, L. O., and Snider, O. E., U.S. Patent 3, 141,036, July 14, 1964.

Wojcik, B., and Adkins, H., *J. Am. Chem. Soc.*, **56**, 2419 (1934).

Yao, H.-C., and Emmett, P. H., *J. Am. Chem. Soc.* **81**, 4125 (1959).

Young, V. V., U.S. Patent 2,864,863, Dec. 16, 1958.

Zajcew, M., *J. Am. Oil Chemists' Soc.* **37**, 11 (1960).

Zhanalinova, A. N., and Sokol'skii, D. V., *Tr. Inst. Khim. Nauk, Akad. Nauk Kaz. SSR* **2**, 222, (1958).

4

Acetylenes

Catalytic hydrogenation of acetylenes proceeds predominantly stepwise, the intermediate olefin being, with few exceptions, very largely of *cis* configuration:

$$\text{Acetylene} \xrightarrow{\text{H}_2} \text{Olefin} \xrightarrow{\text{H}_2} \text{Paraffin}$$

It has been found experimentally that the absolute and relative rates of each step, measured in competition, may vary with catalyst, solvent, inhibitor, temperature, agitation, and amount of catalyst and substrate. Despite the many variables, it is usually possible to achieve good to excellent yields of either the olefin or paraffin without much difficulty. Acetylenes are in general, much more strongly adsorbed than the corresponding olefin. When this is the case, very little olefin will be hydrogenated as long as the acetylene is present, since the acetylene will occupy preferentially the available catalytic sites. For the same reason, other easily reduced functional groups, such as aromatic nitro, may remain unchanged during hydrogenation of acetylenes (Hennion and Barrett, 1957). A few acetylenes on partial hydrogenation afford only mixtures of unchanged starting material and completely saturated product with little or no intermediate olefin (Takei and Ono, 1942b; Berkowitz and Rylander, 1959).

Acetylenes carrying adjacent oxygen functions form a readily available and synthetically important group of compounds whose hydrogenation has been studied extensively, especially by Russian workers (Sokol'skii, 1964). Reduction of these compounds to the corresponding olefins or paraffins is complicated by varying degrees of concomitant hydrogenolysis of the oxygen function. The extent of hydrogenolysis depends on a great many variables, but conditions can usually be found so that it may be adequately controlled.

I. CATALYTIC METAL

Acetylenes have been hydrogenated over all six platinum metals, but palladium and to a lesser extent platinum are by far the most commonly

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used. A number of comparisons of catalysts in hydrogenation of acetylenes has been made. The conclusion was reached, in a study of the hydrogenation of acetylene over palladium-, platinum-, and rhodium-on-carbon, that apart from the activity of the metals, which falls in the order palladium > platinum > rhodium, the metals were not exceptionally different in behavior (Bond *et al.*, 1958). In another study on the hydrogenation of acetylene, methylacetylene, and dimethylacetylene, the order of decreasing selectivity assigned was: palladium > rhodium ≥ platinum > ruthenium > osmium > iridium (Bond *et al.*, 1962). Freidlin and Kaup (1963) proposed the order, palladium black > platinum black > rhodium black > Raney nickel > Raney cobalt, for decreasing selectivity in hydrogenation of terminal acetylenes; and the order, palladium black > Raney nickel > platinum black > Raney cobalt > rhodium black, for decreasing selectivity in hydrogenation of internal acetylenes.

Palladium catalysts are generally considered to be more selective than platinum catalysts in hydrogenation of acetylenes (Johnson, 1946; Siegel and Smith, 1960). For example, hydrogenation of dialkylethynylcarbinols over palladium gave exclusively the olefin after absorption of one equivalent of hydrogen, but over platinum the product was about 15% unchanged substrate, 70% olefin, and 15% saturated alcohol (Nazarov *et al.*, 1946). The selectivity shown by a catalyst cannot be separated from the substrate and, in some reductions, platinum is as selective as palladium (Nikitin and Timofeeva, 1957); in still others, platinum is more selective than palladium. Hydrogenation of di(Δ^2-cyclopentyl)acetylene over platinum afforded, after absorption of three moles of hydrogen, 1,2-dicyclopentylethene, whereas under similar conditions palladium produced a mixture of unsaturated compounds containing mainly 1,2-dicyclopentylethene and 1-(1-cyclopentenyl)cyclopentylethane (Plate and Stanko, 1960).
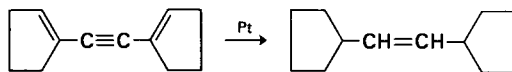
In practice most hydrogenations of acetylenes are carried out over palladium, frequently in conjugation with various modifiers that increase the selectivity. Under special circumstances, rhodium may prove unusually effective (Tedeschi and Clark 1962).

A. CATALYST ACTIVITY

The activity of platinum metal catalysts in acetylene hydrogenations varies widely. Comparative rates for hydrogenation of 2-methyl-3-butyn-2-ol over each platinum metal are given in Table I. The rhodium rate curve was

TABLE I

HYDROGENATION OF 2-METHYL-3-BUTYN-2-OL[a]

Catalyst	Rate (ml H_2/minute)	
	1st mole H_2	2nd mole H_2
5% Palladium-on-carbon	10	13
5% Platinum-on-carbon	3	5
5% Rhodium-on-carbon	1	8[b]
5% Ruthenium-on-carbon	0.0	—
5% Iridium-on-carbon	0.1	—
5% Osmium-on-carbon	0.0	—
Platinum oxide	12	15

[a] Each experiment was done with 10 mg catalyst, 3 mmoles substrate, and 100 ml absolute ethanol at room temperature and pressure.
[b] The rate changed abruptly at 160% of one mole absorbed.

of peculiar shape, for the change in rate occurred at a point far removed from the usual point of inflection, in the neighborhood of one mole of hydrogen absorbed. The shape of this curve hinted at poor selectivity, but analysis of the product after absorption of one mole of hydrogen showed the material to be substantially olefinic, as was also the case in the palladium- and platinum-catalyzed reductions. The absolute and relative rates of hydrogenation for the first and second mole of hydrogen absorbed were found to vary with the amount of catalyst and also with the carrier (Rylander and Himelstein, 1964).

B. AMOUNT OF CATALYST

The absolute and relative rates of hydrogenation of acetylenes and the resulting olefins seem to be unusually sensitive to the amount of catalyst (Sokol'skii, 1964). The rate ratio of hydrogenation to other side-reactions may also change with the amount of catalyst used (Csuros et al., 1951; Schinz, 1955). An example of the effect of the amount of catalyst on the relative rates of reduction of an acetylene and the intermediate olefin is the work of Gensler and Thomas (1951) on hydrogenation of octadecadiyn-9,12-oic acid over 5% palladium-on-strontium carbonate.

$$CH_3(CH_2)_4C\equiv CCH_2C\equiv C(CH_2)_7COOH \longrightarrow$$
$$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7COOH \longrightarrow CH_3(CH_2)_{16}COOH$$
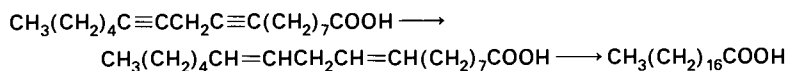
With 10 mg catalyst and 0.348 mmole of substrate in 20 ml ethanol the rates for the acetylene and olefin reductions were 0.8 and 0.025 ml hydrogen

per minute, respectively. However, when the substrate was increased to 1.8 mmoles and the catalyst to 45 mg in 45 ml ethanol, the rate of absorption of the first stage increased 3.75 times (roughly as might be expected), while the rate for the second stage increased 28 times. Part of the change in rate ratio may have been caused by the increase in amount of substrate. It was found, for instance, in hydrogenation of the sodium salt of propiolic acid over platinum that as the substrate concentration increased the rate of hydrogenation of acetylene decreased, while that of the olefin increased (Sokol'skii and Dunina, 1960). The effect of amount of catalyst on rate has been discussed at some length by Sokol'skii (1964).

The effect of temperature on rate may also be related to the amount of catalyst. In the presence of 1.4 mg palladium per ml solution, tetramethyl-butynediol and bis(hydroxycyclopentyl)acetylene were reduced twice as fast at 25°C as at 15°C, but this change in temperature had little effect on the rate of reduction of tetraphenylbutynediol or tetraethylbutynediol, unless the concentration of palladium was raised to 10–20 mg per ml (Levinzon, 1957).

II. MODIFIED CATALYST SYSTEMS

Platinum metal catalysts are used in hydrogenation of acetylenes fre-quently in conjugation with a modifier whose function is to alter the selec-tivity or stereochemistry of hydrogenation or to inhibit side-reactions. Considerable effort has been expended in a search for modifiers; a brief examination of patent literature revealed that a goodly portion of all elements as well as a considerable number of compounds have been claimed or taught to be suitable additives. So many modifiers of widely diverse types have been found to give improved performance in hydrogenation of acetyl-enes that one is inclined to the view that modifiers may function in part by increasing the availability of hydrogen at the catalyst surface, a consequence of the generally lower rate of hydrogenation. However, all additives are not equal in effectiveness, and rates of hydrogenation do not necessarily parallel selectivity.

A. METAL ADDITIVES

Many metal additives have been found that will alter the characteristics of platinum metal catalysts in acetylene hydrogenation. The additives may be incorporated in the catalyst as it made, or added subsequently to the pre-formed catalyst at the time of use. A suitable level of modifier is frequently of the order of one atom of metal additive to one atom of platinum metal,

but different additives show extreme variations in the extent to which they may influence the reduction. For instance, zinc was effective at the level of one atom of zinc per atom of palladium in 5% palladium-on-carbon in improving the selectivity of hydrogenation of 2-methyl-3-butyn-2-ol, and the ratio could be increased to as much as 40:1 without too adverse an effect on the rate. On the other hand, lead, also effective and useful in the same reduction at a 1:1 ratio, almost completely poisoned this catalyst at a 2:1 level. The optimum ratio of additive to platinum metal may change with a change in method of preparing the catalyst, with catalyst carrier, and with the substrate.

An evaluation of the effect of an additive on catalyst performance may be complicated by a gradual alteration in the catalyst. For instance, under certain conditions hydrogenation of 2-methyl-3-butyn-2-ol was complete in about 10 minutes. Addition of 10 atoms of gold, as gold chloride, to the system so inhibited the catalyst that in 200 minutes an identical reduction was only 8% complete. This long, slow hydrogenation proved to be only an induction period, for shortly thereafter the reduction picked up speed and hydrogenation of the substrate was complete within the next 25 minutes. More substrate, added to the system, was reduced at the fast terminal rate (Rylander and Himelstein, 1964).

Ruthenium has been used as a modifier in hydrogenation of acetylenic glycols. Under the conditions used, ruthenium had no catalytic activity toward butynediol-1,4, but when coprecipitated with palladium produced a substantial synergistic effect. The rates of hydrogenation and the moles of hydrogen absorbed are shown in Table II. Absorption in excess of two moles is indicative of hydrogenolysis and formation of butanol. The rate curves were all zero order except for tailing near the end, during which a slow

TABLE II

HYDROGENATION OF BUTYNEDIOL-1,4 OVER PALLADIUM AND RUTHENIUM[a]

Catalyst	Metal (mg)	Methanol		Acetic acid	
		ml H_2/min	moles H_2	ml H_2/min	moles H_2
5% Pd-on-carbon	15	20	2	64	2
3.4% Pd, 1.6% Ru-on-carbon	15	47	3	27	2
2.5% Pd, 2.5% Ru-on-carbon	15	100	3	37	2
4.0% Pd, 1.0% Ru-on-carbon	15	26	2.5	24	2
5% Pd-on-carbon	7.5 ⎫	32	2	40	2
5% Ru-on-carbon	7.5 ⎭				

[a] Each experiment was done with 300 mg catalyst, 200 mg butynediol, and 100 ml solvent at atmospheric pressure and room temperature.

absorption occurred in excess of that indicated in Table II. Partial sub-
stitution of palladium by ruthenium led to catalysts that showed increased
activity in methanol but less activity in acetic acid, and produced butanol
instead of butanediol in methanol solvent. Of particular interest is the
synergistic effect obtained just on mixing 150 mg each of 5% palladium-
on-carbon and 5% ruthenium-on-carbon. On a weight of palladium basis,
the mixed catalyst was much superior to palladium alone; ruthenium alone
was completely inactive. The course of the reduction was influenced also by
the catalyst-to-substrate ratio. When less catalyst and more substrate were
used, no hydrogenolysis occurred, the rate curves were complex, but the
synergistic effects remained (Rylander and Cohn, 1961).

   A few examples from the literature will suffice to illustrate the variety of
metal additives that have been used in hydrogenation of acetylenes. A
palladium–copper-on-carbon catalyst, selective for hydrogenation of 1,4-
butynediol, was made by shaking a copper acetate solution with 5%
palladium-on-carbon at 40°C and 75 psig (Hort, 1960). A palladium–copper-
on-alumina catalyst for the same use was prepared by treating a palladium-
on-alumina catalyst with copper acetate and hydrazine hydrate (British
Patent 832,141). A selective catalyst for hydrogenation of acetylenic alcohols
to olefinic alcohols was made from kieslguhr, palladium chloride, and ferric
chloride (Reppe et al., 1955). Selective reduction of acetylene to olefin was
achieved in derivatives of α-ethynyl-β-ionol with mixtures of palladium-on-
carbon and palladium-on-calcium carbonate catalysts inhibited by zinc
acetate and diethylamine (Oroshnik, 1958). A selective catalyst for hydro-
genation of acetylenic to olefinic alcohols has been made from calcium
carbonate, stannous chloride, and palladium chloride (French Patent
1,224,182). Lead-inhibited palladium-on-calcium carbonate catalysts
(Lindlar, 1952) have been widely used in selective hydrogenations with
excellent results (Crombie, 1955; Seher, 1955). Selective catalysts for hydro-
genation of acetylenes can be made in many ways and it is usually possible
without much effort to obtain such a catalyst, which, if not optimum, is at
least good enough.

B. OTHER ADDITIVES

   Acetylenes are frequently hydrogenated in the presence of nonmetallic
additives such as amines, sulfur compounds, acids, and bases. Often metallic
and nonmetallic modifiers are used together. Perhaps the best known of
such systems is the Lindlar catalyst further modified by addition of quinoline.
Other amines have been used in selective hydrogenations, but all amines are
not necessarily equivalent in action. For instance, selective hydrogenation
of 1,4-butynediol was achieved with palladium-on-calcium carbonate

inhibited by quinoline, but not pyridine or piperidine (Fukuda and Kusama, 1958). In a further example, the selectivity of reduction of vinylacetylene to butadiene over colloidal palladium was increased by lead or copper acetate and by quinoline, and decreased by pyridine, aniline, and diethylamine (Bal'yan and Borovikova, 1959a).

Amines have been used as solvents in selective hydrogenation of acetylenes (Bowers et al., 1958; Chase and Galender, 1959). Ethinyl androstenediol (I) was reduced selectively to vinyl androstenediol (II) over palladium-on-calcium carbonate in pyridine solvent. The ethyl derivative (III) was obtained by reduction over 5% palladium-on-carbon in ethanol (Hershberg et al., 1951). This paper contains a number of interesting examples of selective reduction.

CH=CH₂   C≡CH
OH   OH˙

pyridine Pd/CaCO₃   ethanol Pd/C
95%   99%

(II)   (I)

C₂H₅
OH

(III)
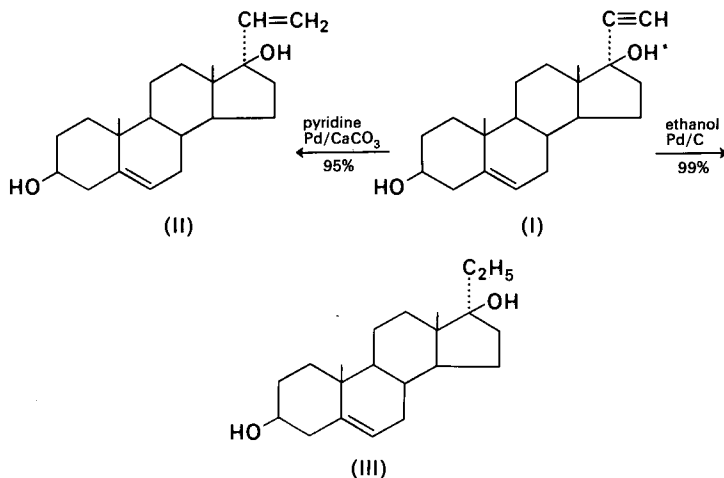
The selectivity of an acetylene reduction may be strongly influenced by the presence of small amounts of acid or alkali. Small amounts of either phosphoric acid or p-toluenesulfonic acid (0.10 gm acid per mole of acetylenic diol) resulted in the formation of large amounts of tetrahydrofurans and hydrocarbons during reduction of 1,4-acetylenic glycols over 5% palladium-on-carbon. In the absence of added acid no furans were found (Tedeschi, 1962). Hydrogenolysis that occurs readily even in the absence of acid during reduction of 1,4-acetylenic glycols can be eliminated by carrying out the reduction in the presence of very small amounts of base. A suitable system for converting acetylenic 1,4-glycols to the corresponding olefinic glycols is a mixture of 0.50 mole of acetylenic 1,4-glycol, 100 ml n-heptane, 1.0 gm 5% palladium-on-carbon, and 0.025–0.05 gm powdered potassium hydroxide, sodium hydroxide, or triethylamine. For relatively insoluble glycols, methanol or isopropanol may be preferred to heptane. Selective hydrogenation of this system proceeded readily at 60–65°C and 30–55 psig

(Tedeschi, 1962). Reduction of the acetylene to olefin proceeded rapidly over palladium-on-carbon in the absence or presence of base, but the olefin-to-paraffin stage of the reduction was inhibited by base. Sodium hydroxide was found to be a stronger inhibitor than potassium hydroxide, and consequently potassium hydroxide is preferred when the goal of the hydrogenation is the saturated glycol. Potassium carbonate was about one tenth as effective as potassium hydroxide in preventing hydrogenolysis; potassium bicarbonate was without effect.

Tedeschi and Clark (1962) applied the use of bases to selective semi-hydrogenation of ethynylcarbinols to vinylcarbinols. Palladium, platinum, and rhodium in the presence of various bases were evaluated. In the selective reduction of 3-methyl-1-butyn-3-ol, rhodium-on-carbon inhibited by sodium methoxide proved to be superior to palladium or platinum, but this rhodium–methoxide system was not further examined. The authors found the catalyst system, palladium-on-barium sulfate in the presence of powdered potassium hydroxide, to be generally the most useful studied. Hydrogenations over palladium-on-carbon inhibited by base did not stop spontaneously after absorption of one equivalent of hydrogen, but nonetheless excellent yields of vinylcarbinols could be obtained if the reduction were interrupted. Better products were obtained by using base-modified palladium than by using Lindlar catalyst or very small amounts of palladium-on-barium carbonate (Hennion et al., 1956). In the absence of a basic modifier, the half-hydrogenated product always contained varying amounts of unreduced acetylenic carbinol and an equal amount of saturated material.

The presence of base also effected a significant decrease in rate of hydrogenation after absorption of one mole of hydrogen. Typical conditions for selective semihydrogenation were: 1.0 mole of tertiary acetylenic carbinol, 100 ml n-hexane or 20–40°C petroleum ether, 0.15 gm 5% palladium-on-carbon, -barium carbonate, -calcium carbonate, or -barium sulfate, and 0.30 gm powdered 90–100% potassium hydroxide. The reaction temperature was maintained at 25–30°C, which necessitated occasional cooling.

C. ROLE OF MODIFIER

There is evidence to suggest that some nonmetallic additives may function through complex formation with the substrate. For instance, Bal'yan (1951) examined the action of a variety of inhibitors, such as chlorobenzenes and phenylthiocyanates, on the reduction of acetylenic glycols, and presented evidence to show that the inhibitor does not act on the catalyst but forms a compound with the substrate. Tedeschi (1962) reached a similar conclusion regarding the role of potassium and sodium hydroxides in hydrogenation of acetylenic glycols. Complex formation was indicated by the observation

that the powdered base is completely soluble in hexane solutions containing an equivalent of acetylenic glycol. Further, anhydrous potassium hydroxide interacts with 2,5-dimethyl-3-hexyne-2,5-diol in dry inert solvent to afford a white, stable, one-to-one mole complex. A similar complex was formed with the corresponding olefin but not with the saturated diol. These complexes behave differently in hydrogenation than the compounds formed by interaction of potassium metal with acetylenic glycol dissolved in inert solvent.

Adventitious Modifiers

The course of an acetylene hydrogenation may be influenced strongly by the presence of various impurities that enter the system inadvertently. For instance, hydrogenation of highly purified 9-octadecynedioic acid over 10% palladium-on-carbon in absolute methanol afforded, after absorption of one equivalent of hydrogen, a mixture of products, whereas hydrogenations using a somewhat less pure substrate stopped automatically after absorption of one equivalent, and afforded 9-octadecenedioic acid in nearly quantitative yield (Gensler and Schlein, 1955). When the highly purified material was reduced with catalysts recovered from reductions using less pure material, absorption again stopped at one mole, and gave 9-octadecenedioic acid in nearly quantitative yield. Evidently the less pure substrate contained a highly effective catalyst modifier. Similar modifiers may enter the system in the solvent, in a quinoline additive, or from the reactor itself. Adventitious modification of the catalyst in this way undoubtedly accounts for some of the conflicting reports in the literature.

The hydrogenation of 1,1-diethoxy-5-hydroxyhex-2-yne (IV) was strongly influenced by traces of impurity, the nature of which was deduced from the products of the reaction. Hydrogenation of IV over 10% palladium-on-carbon or over Lindlar catalyst in hexane was erratic; in some cases the product was a dihydropyran (V) and in others 1,1-diethoxy-5-hydroxyhexene-2 (VI). Since the latter compound could be readily converted to the pyran by acid, it was felt that the erratic results could be attributed to chance traces of acid; indeed, when a trace of quinoline was added to the system the acyclic olefin was obtained consistently (Newman, 1964).

$$CH_3-\underset{\underset{\displaystyle(IV)}{}}{\overset{\overset{\displaystyle OH}{|}}{CH}}-CH_2-C\equiv C-CH(OC_2H_5)_2 \quad \underset{H_2}{\overset{H_2,\ H^+}{\rightleftarrows}}$$

$$CH_3 \overset{\displaystyle (V)}{\underset{O}{\diagup \diagdown}} OC_2H_5$$

$$CH_3\underset{\underset{\displaystyle OH}{|}}{CH}-CH_2-CH=CH-CH(OC_2H_5)_2$$

(VI)
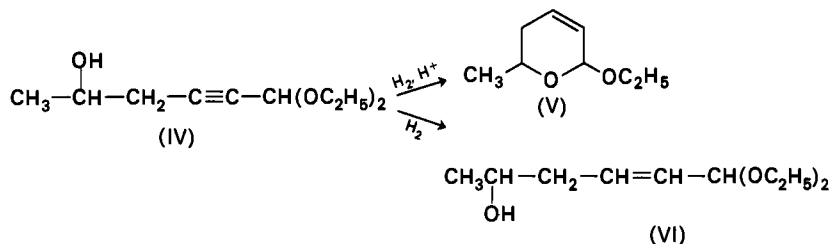
III. STEREOCHEMISTRY

Hydrogenation of disubstituted acetylenes to olefins usually give pre-dominantly the thermodynamically less stable *cis* isomer accompanied by various lesser amounts of *trans* isomer. Whether the *trans* isomer is a primary product is often a moot question (Burwell, 1957), for *cis* and *trans* isomers are readily interconvertible over platinum metal catalysts in the presence of hydrogen. Burwell and Hamilton (1959), studying the hydrogenation of dimethylacetylene over a 0.03% palladium-on-alumina catalyst, concluded that the initial product was almost exclusively *cis*-2-butene, and that after all the acetylene was gone the olefin then isomerized to *trans*-2-butene. Other workers have obtained evidence to show that *trans* isomer may be formed directly in hydrogenation of acetylenes, and a mechanistic inter-pretation of the process has been suggested (Bond, 1962).

A. CATALYSTS AND CONDITIONS

The stereospecificity of acetylene reduction depends in part on the catalytic metal. Freidlin and Kaup (1963) established the following order of decreasing stereospecificity in hydrogenation of 2-pentyne: palladium black > Raney nickel > platinum black > rhodium black > Raney cobalt. Palladium, especially when modified by an additive, is widely used to obtain olefins of predominantly *cis* configuration. The most popular catalyst of these is the Lindlar catalyst, palladium-on-calcium carbonate modified by addition of lead (Lindlar, 1952). Bismuth also makes a suitable modifier (Lindlar, 1954). The catalyst is frequently used with small amounts of quino-line (Lindlar, 1952), which increases selectivity. For instance, 1.1 gm 10-hydroxy-7-hexadecynoic acid in 10 ml methanol containing a few drops of quinoline was reduced over 0.5 gm palladium–lead-on-calcium carbonate to afford, after absorption of one equivalent of hydrogen, 10-hydroxy-*cis*-7-hexadecenoic acid (Jacobson *et al.*, 1961). The quality of quinoline may be important. In other work, pure synthetic quinoline was satisfactory whereas quinoline from coal tar was unsuitable (Cram and Allinger, 1956). The amount of quinoline may also affect the results. Hydrogenation of stearolic acid over Lindlar catalyst in ethyl acetate containing quinoline gave olelic acid containing 5% of the *trans* olefin; with double the amount of quinoline the *trans* isomer was only 1–2% (Baker *et al.*, 1955).

The amount of catalyst and the catalyst support may have a marked effect on the percentage of *trans* isomer. Partial hydrogenation of undec-4-yne in cyclohexane over 10% (by weight) and 17.4% (by weight), based on sub-strate, of 10% palladium-on-carbon afforded 68% and 31% *trans* isomer in the resulting olefin, respectively. In ethyl acetate solvent, the *trans* olefin

content from hydrogenation over about 10% (by weight), based on substrate, of 10% palladium-on-calcium carbonate, 10% palladium-on-barium sulfate, and 10% palladium on-carbon was 63%, 40%, and 32%, respectively. By addition of triethylamine to the palladium-on-carbon-catalyzed reductions, the *trans* olefin content was decreased from 32% to 17%, but only by the use of Lindlar catalyst with quinoline could small percentages (4%) of *trans* olefin be obtained. The amount of *trans* isomer formed in reduction of undec-4-yne over unmodified palladium catalysts is unusually high. It was shown in this work that, when very small amounts of catalysts were used, *cis*-undec-4-ene was transformed with hydrogen present to a mixture containing about 70% *trans* isomer with virtually no saturation of the double bond. The *trans* isomer, on the other hand, could not be isomerized in this way, for it underwent rapid hydrogenation. The results imply that, in a mixture of *cis* and *trans* isomers, the *cis* isomer preferentially occupies the available hydrogenation sites and thus inhibits hydrogenation of the *trans* isomer (Dobson *et al.*, 1961).

Marked variations in the *cis-trans* isomer ratio are achieved sometimes by minor changes in the ratio of reactants. Mondon (1952) obtained either predominantly the *cis* or *trans* olefin on hydrogenation of 1-(4-hydroxy-4-methylpentynyl)cyclohexanol by changing the catalyst-to-substrate ratio and the amount of quinoline modifier. The *cis* olefin was obtained by hydrogenation of 0.5 gm substrate over 0.5 gm 5% palladium-on-carbon in 10 ml methanol containing 2 drops of quinoline, whereas 2.0 gm substrate and 1 drop of quinoline similarly reduced gave largely the *trans* olefin.
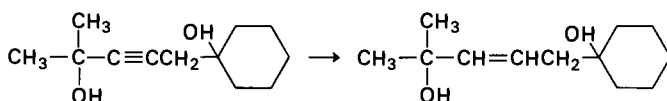
Certain hydrogenations of acetylenes seem unusually sensitive to the presence of alkali. Hydrogenation of butyne-1,4-diol generally gives *cis*-but-2-ene-1,4-diol, but in the presence of alkali a high proportion of *trans* isomer is found. Acetylenedicarboxylic acid and its ester afford predominantly the *trans* olefins under alkaline conditions. The fumarate is obtained from hydrogenation of monopotassium acetylenedicarboxylate in water or aqueous alkali (McQuillin and Ord, 1959).

B. AGITATION AND RATE OF REDUCTION

The percentage of *trans* isomer formed in partial hydrogenation of acetylenes may depend on the agitation and rate of reduction. For instance, hydrogenation of 1-chloro-4,7,10,13-nonadecatetrayne (VII) under carefully controlled conditions afforded the all-*cis* tetraene (VIII) in 80% yield

(Ege *et al.*, 1961). The hydrogenation was carried out after adding 3.26 gm freshly distilled VII in 50 ml hexane to 3.26 gm Lindlar catalyst in 550 ml hexane containing 0.82 gm synthetic quinoline. The rate of hydrogen absorption, controlled by the rate of magnetic stirring, was maintained at 5–6 ml per minute. After absorption of about four equivalents of hydrogen the rate dropped spontaneously to a low level and the reaction was discontinued. Higher rates of hydrogenation gave increasingly greater amounts of *trans* isomer. The amount of *trans* isomer also depended on the amount of quinoline, on the activity of the catalyst, and on the temperature of reduction. Successful reductions required the use of freshly distilled tetrayne; very little hydrogenation occurred when the substrate was 2 days old (Gensler, 1963).

(VII) $CH_3(CH_2)_4C{\equiv}CCH_2C{\equiv}CCH_2C{\equiv}CCH_2C{\equiv}C(CH_2)_3Cl \longrightarrow$

(VIII) $CH_3(CH_2)_4CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_3Cl$
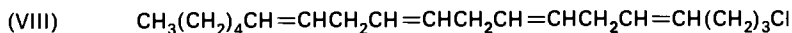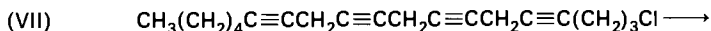
Other workers have also noted the effect of rate of reduction on the product. Polyesters, prepared by condensing diols with acetylenedicarboxylic acid, were partially hydrogenated, as a 2% solution in acetone, over a palladium–lead catalyst. If the hydrogenation rate was high the polyester had a *cis* configuration, and if low the *trans* configuration (Batzer and Weissenberger, 1954). In a more general study, Ott and Schroter (1927), using catalysts modified by partial poisoning, reached the same conclusion; faster rates give more *cis* isomer, slower rates more *trans*.

C. TEMPERATURE

The percentage of *trans* isomer formed on hydrogenation of acetylenes may depend also on the temperature. Partial hydrogenation of 3-hexyn-1-ol over platinum oxide at $-19°C$ afforded a mixture of 40% *trans*-3-hexen-1-ol and 60% of an isomerized compound, 4-hexen-1-ol, of uncertain stereochemistry; at 60°C or above only 4-hexen-1-ol was obtained (Takei and Ono, 1942a). The isomerization seems remarkably specific; the system would provide an interesting vehicle for mechanistic studies.

$$CH_3CH_2C{\equiv}CCH_2CH_2OH \longrightarrow$$
$$CH_3CH_2CH{=}CHCH_2CH_2OH + CH_3CH{=}CHCH_2CH_2CH_2OH$$
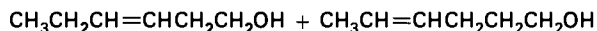
The effect of temperature on the products formed, in partial hydrogenation of three disubstituted acetylenes over palladium-on-barium sulfate and over platinum black, is shown in Table III. Little selectivity was shown in partial hydrogenation of acetylenedicarboxylic acid over palladium-on-barium sulfate at $-18°C$; the products obtained on half-hydrogenation were succinic acid and unchanged starting material (Takei and Ono, 1942b).

TABLE III

EFFECT OF TEMPERATURE IN PARTIAL HYDROGENATION OF ACETYLENES

Substrate	Catalyst	Temperature (°C)	Product
Acetylene-dicarboxylic acid	Pd-on-BaSO$_4$	−18 100	Succinic acid Maleic acid
	Pt black	−18 100	Succinic acid Succinic acid
Phenylacetylene-carboxylic acid	Pd-on-BaSO$_4$	−18 100	20–25% *trans* isomer 0% *trans*, 100% *cis*
	Pt black	−18 100	25–33% *trans* isomer 25–28% *trans* isomer
p-Methoxyphenyl-acetylenecarboxylic acid	Pd-on-BaSO$_4$	−18 100	20–25% *trans* isomer 15–20% *trans* isomer
	Pt black	−18 100	23–25% *trans* isomer 24–25% *trans* isomer

At 100°C, reduction over palladium-on-barium sulfate afforded maleic acid. The dependence of selectivity and stereochemistry on temperature is seen to vary with both the catalyst and substrate. In other compounds (3-hexyn-1-ol, stearolic acid, and behenolic acid) a clearer trend emerged, and Takei and Ono (1942b) favored the generality that *cis* forms are produced at high temperature, *trans* forms at low temperature.

IV. DIACETYLENES

Diacetylenes have been reduced stepwise to an enyne, a diene, an olefin, and a hydrocarbon. The selectivity of reduction at each step depends in large measure on whether the diacetylene is conjugated; high selectivity is more difficult to achieve in a conjugated system. Essentially only one hydrocarbon was obtained at each stage of hydrogenation of the nonconjugated undeca-1,7-diyne (IX) over 10% palladium-on-carbon, the products in sequence being undec-1-en-7-yne (X), undeca-1,7-diene (XI), and undec-4-ene (XII). The central double bond in undeca-1,7-diene was predominantly

$$CH_3(CH_2)_2C\equiv C(CH_2)_4C\equiv CH \longrightarrow CH_3(CH_2)_2C\equiv C(CH_2)_4CH=CH_2$$
$$\text{(IX)} \hspace{5cm} \text{(X)} \downarrow$$
$$CH_3(CH_2)_2CH=CH(CH_2)_5CH_3 \longleftarrow CH_3(CH_2)_2CH=CH(CH_2)_4CH=CH_2$$
$$\text{(XII)} \hspace{5cm} \text{(XI)}$$
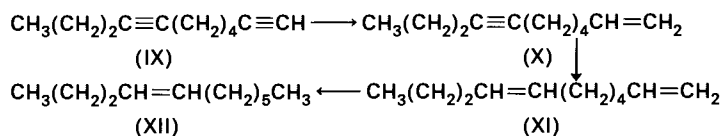
of *cis* configuration, but the next product, undec-4-ene, contained about 50% of the *trans* isomer.

The preference for hydrogenation of a terminal triple bond to an internal one, and of an internal acetylene to an external olefin, was maintained even when the triple bonds concerned were in separate molecules. In partial hydrogenation of an equimolar mixture of oct-1-yne and oct-4-yne, the products after absorption of one equivalent of hydrogen were oct-1-ene and unchanged oct-4-yne, and after absorption of two equivalents oct-1-ene and oct-4-ene (Dobson *et al.*, 1961).

Various macrocyclic nonconjugated diynes and tetraynes have been reduced smoothly to the corresponding *cis* polyenes over Lindlar catalyst; the absorption virtually stopped at the theoretical quantity of hydrogen. On the other hand, similar reductions of conjugated diynes continued on past theoretical absorption, but even so some starting material remained and no definite partial reduction products could be obtained (Dale *et al.*, 1963).

CATALYSTS

Some pronounced effects of catalyst on the products of reduction of diacetylenes have been reported. Reduction of the macrocyclic diyne lactone (XIII) over platinum in ethyl acetate afforded the saturated lactone (XIV). Over Lindlar catalyst, the reduction slowed considerably after absorption of two equivalents of hydrogen to afford the dienolide (XV) in 86% yield. With 10% palladium-on-carbon, a marked decrease in rate occurred after absorption of three equivalents of hydrogen, and the product at this stage was a mixture of 27% Δ^{10}, 10% Δ^{11}, and 20% Δ^{12} monoenes and 32% saturated lactone (McCrae, 1964).
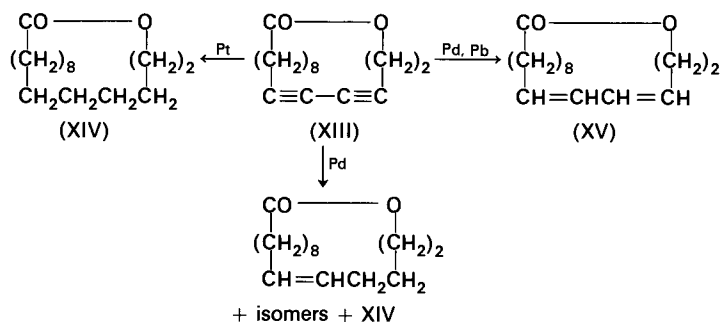
It appears that partial hydrogenation of diacetylenes can best be achieved over palladium and a more complete hydrogenation over platinum. The

diene, 2,9-dimethyl-5,6-diphenyl-3,7-decadiene-2,5,6,9-tetrol, was obtained from the corresponding diacetylene when reduction over palladium in ethyl acetate stopped spontaneously after absorption of two equivalents of hydrogen, whereas over platinum four equivalents were rapidly absorbed (Zal'kind and Zhuravleva, 1948). Similarly, reduction of 2,7-di-*p*-tolyl-3,5-octadiyne-2,7-diol with colloidal palladium gave the octadiene and over platinum the octane (Zal'kind and Iremadze, 1948). The selectivity of partial hydrogenation of diacetylenes may be increased by use of suitable modifiers.

V. VINYLACETYLENES

Selective hydrogenation of vinylacetylenes to dienes is more difficult than selective hydrogenation of an isolated triple bond to a double bond. Attempts to reduce selectively 6, 9-dimethyltetradecadiene-5,9-ine-7 in glacial acetic acid over platinum oxide by absorption of one or two moles of hydrogen failed; the product was a complex mixture showing no point of preferential absorption (Blomquist and Marvel, 1933). Selective hydrogenation of conjugated enynes to dienes is easier if the triple bond is in a terminal position (Bal'yan and Borovikova, 1959b).

A quantitative measure of selectivity in partial hydrogenation of some vinylacetylenes over Lindlar catalyst, further inhibited by quinoline, has been obtained by Marvell and Tashiro (1965). The compounds and reaction examined were:

(XX)
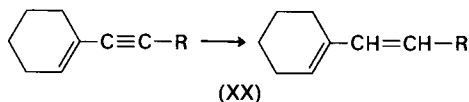
(XVI)   R = H
(XVII) R = $-CH_3$
(XVIII) R = $-C_2H_5$
(XIX)   R = $-CH=CH_2$

Each reduction, carried out in petroleum ether, was interrupted after absorption of one equivalent of hydrogen and the resulting products were analyzed by gas chromatography. The corresponding diene (XX) was obtained in 80–90% yield when the substrate was XVI, XVII, or XVIII, but hydrogenation of XIX gave a complex mixture consisting of 47% *cis*- and 7% *trans*-$C_6H_9CH=CH-CH=CH_2$, 13% *cis*- and 8% *trans*-$C_6H_9CH=CH-C_2H_5$, 8% $C_6H_9C\equiv C-C_2H_5$, 4% $C_6H_9CH_2CH_2C_2H_5$, 8% $C_6H_9C\equiv C-CH=CH_2$, and 5% unidentified material. Each of the three enynes (XVI–XVIII) studied was reduced exclusively at the triple bond.

Selectivity was somewhat less than that observed with isolated triple bonds, as some complete saturation of the triple bond occurred even while the enyne was still present. The poor selectivity obtained in hydrogenation of XIX has a parallel in earlier work (see Marvell and Tashiro, 1965) on partial hydrogenation of dienynes. However, excellent selectivity has been reported in hydrogenation of long, conjugated systems containing an interior triple bond (Akhtar and Weedon, 1959; Isler *et al.*, 1956).

An unusual reduction of a complex vinylacetylene is the conversion of tridehydro[18]annulene (XXI) to [18]annulene (XXII). Both the chemistry of this reduction and the techniques employed have interesting aspects. Hydrogenations over lead–palladium-on-calcium carbonate (Lindlar, 1952) proved to be erratic, and at times the reduction stopped spontaneously before three equivalents of hydrogen were absorbed. Hydrogenation over 10% palladium-on-carbon in benzene gave reproducible yields of XXII, although there was a certain variation in unchanged starting material. Maximum conversion of substrate to product was obtained not after absorption of the stoichiometric three equivalents of hydrogen but after 5–6 molar equivalents had been absorbed. The optimum amount of hydrogen to be absorbed was determined by allowing the reduction to proceed to completion, with aliquots withdrawn at intervals and analyzed for product and unchanged starting material by ultraviolet examination. The actual yield based on unrecovered substrate was higher when less than 5–6 molar equivalents were absorbed, but for preparative purposes it was advantageous to have little unchanged starting material remaining. Under optimum conditions [18]annulene could be obtained in 25% yield.

Catalytic partial hydrogenation of acetylenes leads predominantly to the corresponding *cis* ethylenes, and 18[annulene] would therefore be expected to have 6 *cis* and 3 *trans* double bonds. However, the ultraviolet spectrum indicated, and X-ray structure analysis confirmed, that the product contained 3 *cis* and 6 *trans* double bonds derived by overall *trans* addition of hydrogen. A similar partial hydrogenation of tetradehydro[24]annulene afforded [24]annulene (Sondheimer *et al.*, 1962).

(XXI)   (XXII)
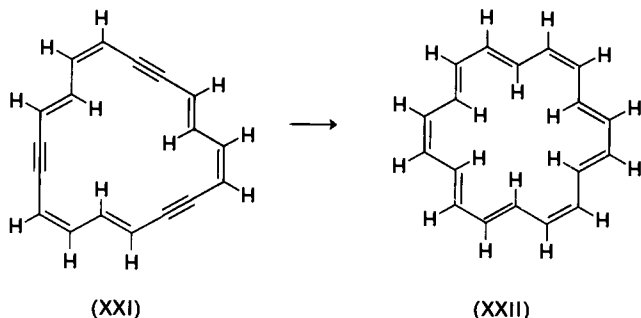
CATALYSTS

Palladium-on-barium sulfate proved more selective than platinum-on-carbon or Raney nickel in hydrogenation of vinylacetylene in liquid phase. This is clearly shown by the data of Table IV, which gives the composition of the product at a point where vinylacetylene had just disappeared. A maximum yield of 22% butadiene was obtained in gas phase reductions along with polymerization products (Albrecht, 1961). The results may also be influenced by the support. In hydrogenation of vinylacetylene to butadiene,

TABLE IV

HYDROGENATION OF VINYLACETYLENE[a]

Catalyst	Products (%)		
	Butadiene	Butenes	Butane
Pd-on-barium sulfate	69	30	1
Pt-on-carbon	48	39	13
Raney nickel	35	42	23

[a] Product analysis made at point of disappearance of vinylacetylene.

palladium-on-barium sulfate was preferred to palladium-on-calcium carbonate, -starch, -bauxite, -kaolin, or -pumice (Rieche *et al.*, 1961). Palladium-on-barium sulfate has been said to be generally superior to Lindlar catalyst for selective hydrogenations (Cram and Allinger, 1956). The differences between palladium and platinum were accentuated in hydrogenation of the substituted vinylacetylenes, 1-(3-buten-1-ynyl)cyclopentanol, diethyl(3-buten-1-ynyl)carbinol, and dipropyl(3-buten-1-ynyl)carbinol. In the presence of platinum black all three compounds absorbed three moles of hydrogen, forming the saturated alcohol, but in the presence of palladium the last two compounds absorbed only two moles of hydrogen. Although there was no break in the hydrogenation rate curve for the first two moles absorbed over palladium, the diene could be obtained if the reduction were interrupted after absorption of one mole (Zal'kind and Boroda, 1945).

$$(C_2H_5)_2\underset{\underset{OH}{|}}{C}-C\equiv C-CH=CH_2 \xrightarrow[H_2]{Pd} (C_2H_5)_2\underset{\underset{OH}{|}}{C}-CH=CH-CH=CH_2 \xrightarrow[H_2]{Pd}$$

$$(C_2H_5)_2\underset{\underset{OH}{|}}{C}-CH=CH-CH_2CH_3 \xrightarrow[H_2]{Pt} (C_2H_5)_2\underset{\underset{OH}{|}}{C}-CH_2CH_2CH_2CH_3$$
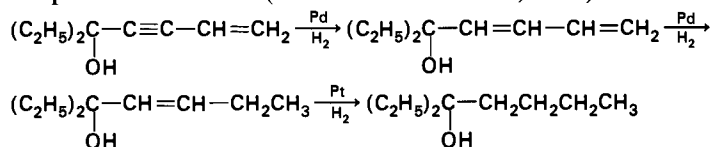
VI. HYDROGENOLYSIS

Hydrogenation of acetylenes carrying adjacent oxygen or nitrogen functions is apt to be accompanied by loss of the function in varying degree.

Loss of oxygen during hydrogenation of a series of 1,4-acetylenic glycols
was convincingly shown to occur predominantly after formation of the
olefinic glycol and before complete saturation (Tedeschi, 1962). Allylic
functions are particularly susceptible to hydrogenolysis, and it is probably
generally true that hydrogenolysis in most acetylene reductions occurs
after formation of the olefin. The influence of substituents was examined
on the extent of hydrogenolysis during complete reduction of a series of
acetylenic glycols; the results are shown in Table V (Tedeschi, 1962a).

TABLE V

$$\text{H{\scriptsize YDROGENOLYSIS}}^a \text{ OF } R-\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}-C\equiv C-\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}-R$$

R	Moles H_2O formed per mole substrate
Methyl	1.13
Phenyl	1.02
Isobutyl	1.00
Ethyl	0.835
Cyclohexyl	0.823
n-Propyl	0.757

^{a} Catalyst: 5% palladium-on-carbon

The percentage of hydrogenolysis decreased steadily in the series methyl,
ethyl, propyl, but an overall generality to encompass all the data is not
evident. With each of these compounds, hydrogenolysis could be reduced
to virtually zero by the presence of 0.05–0.10 gm potassium hydroxide per
mole of substrate (discussed in detail in Section II, "Modified Catalyst
Systems"). Hydrogenolysis of acetylenic carbinols is also diminished by the
presence of base (Tedeschi and Clark, 1962), but hydrogenolysis of carbinols
is usually a minor side-reaction. Substantial hydrogenolysis may accompany
reduction of esters of hindered acetylenic carbinols. The hydrogen phthalate
ester of 3,4,4-trimethylpent-1-yn-3-ol (XXIII) was reduced in ethyl acetate
to the corresponding olefin (XXIV) over Lindlar catalyst, and to the saturated
alcohol (XXV) over platinum oxide. Reduction in both cases was accom-
panied by 20–30% hydrogenolysis (Evans et al., 1963).

$$CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-\underset{\underset{OR}{|}}{\overset{\overset{CH_3}{|}}{C}}-C\equiv CH \longrightarrow CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-\underset{\underset{OR}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH=CH_2 \longrightarrow CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-\underset{\underset{OR}{|}}{\overset{\overset{CH_3}{|}}{C}}-C_2H_5$$

(XXIII)   (XXIV)   (XXV)
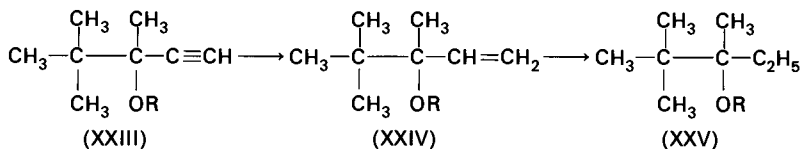
R = phthalate

In certain compounds, hydrogenolysis may occur even after the acetylene is completely saturated. Exhaustive hydrogenation of the diol (XXVI) over palladium-on-calcium carbonate afforded the saturated glycol (XXVII), but hydrogenation of XXVIII gave first the saturated diacetate and, if the reduction were allowed to continue beyond absorption of two moles, an ester group was lost (Nogaideli and Vardosanidze, 1963).

(XXVII)   R = H
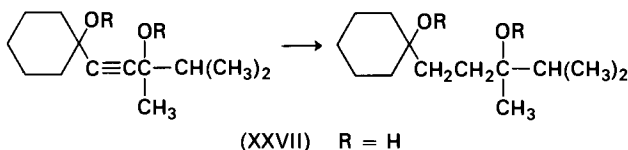
(XXVI)   R = H
(XXVIII) R = COCH$_3$

Hydrogenolysis of epoxides adjacent to acetylenes might be expected to be extensive, inasmuch as even an unactivated epoxide will readily undergo hydrogenolysis. Reduction of the acetylenic diepoxide (XXIX) in ethanol over Lindlar catalyst, and subsequently when the reduction became very slow over a palladium-on-carbon catalyst, afforded about equal amounts of a di-sec-diol (XXX) and a sec-mono-ol (XXXI) (Ghera et al., 1962). Formation of secondary rather than tertiary alcohols implies hydrogenolysis prior to complete loss of the carbon–carbon bond unsaturation. The loss of oxygen leading to XXXI was unexpected; it might imply hydrogenolysis of the epoxide ring in the reverse sense followed by hydrogenolysis of the resulting unsaturated tertiary alcohol, or hydrogenolysis of the epoxide ring at the tertiary carbon followed by isomerization of the carbon–carbon double bond to an allylic position. There is precedent for the hydrogenolysis of 3-acetylenic or ethylenic alcohols. Hydrogenation of hept-3-yne-1,7-diol over 5% palladium-on-barium sulfate afforded a considerable amount of n-heptanol (Crombie and Jacklin, 1957), and hydrogenation of 6-methyloct-3-en-ol afforded 3-methyloctane (Crombie and Harper, 1950).

(XXIX)   (XXX)   (XXXI)
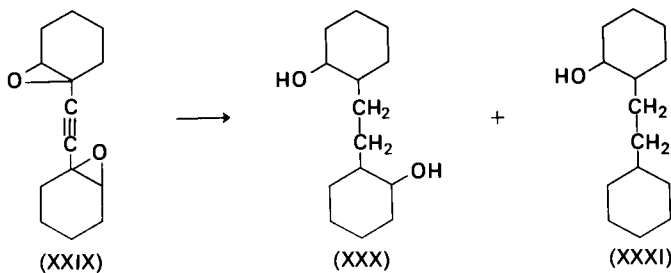
Minor structural variations may have a decisive influence on the course of reduction. Hydrogenation of XXXII over either Raney nickel or 10%

palladium-on-carbon in petroleum ether afforded 2-pyrrolidino-2-methyl-butane (XXXIII), whereas under the same conditions the diethylamino derivative underwent extensive hydrogenolysis. If reduction of either substrate were terminated after absorption of one mole of hydrogen, the corresponding allylic amines could be obtained in good yield; hydrogenolysis evidently occurred after formation of the allylic compound (Hennion and Perrino, 1961).

CH$_3$C—C≡CH   ⟶   CH$_3$CCH$_2$CH$_3$
      | |
     CH$_3$ CH$_3$

(XXXII)   (XXXIII)
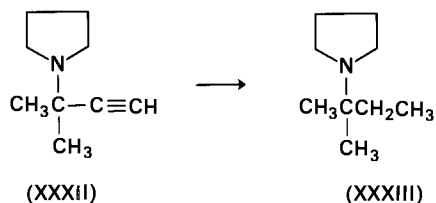
Hydrogenolysis during reduction of hindered acetylenic amines to saturated amines may to a large extent be prevented by hydrogenating the acetylenic amines as hydrochlorides over platinum oxide (Easton *et al.*, 1961). Platinum oxide proved superior to palladium-on-carbon in reduction of XXXIV to the ethyl derivative. Reduction of XXXIV over palladium-on-carbon in ethanol–acetic acid resulted in preferential hydrogenolysis of the dimethylamino group; after absorption of two equivalents of hydrogen, the product contained no basic amine groups. However, reduction over platinum oxide in ethanol–acetic acid give the 17β-dimethylamino-17α-ethyl derivative (Morrow *et al.*, 1965).

N(CH$_3$)$_2$
······C≡CH

· HO

(XXXIV)
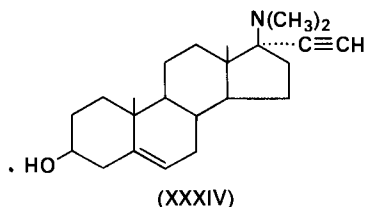
REFERENCES

Akhtar, M., and Weedon, B. C. L., *J. Chem. Soc.* p. 4058 (1959).
Albrecht, H., *Monatsber. Deut. Akad. Wiss. Berlin* 3, 714 (1961).
Baker, B. W., Linstead, R. P., and Weedon, B. C. L., *J. Chem. Soc.* p. 2218 (1955).
Bal'yan, Kh. V., *Zh. Obshch. Khim.* 21, 720 (1951); *J. Gen. Chem. USSR* 21, 793 (1951).
Bal'yan, Kh. V., and Borovikova, N. A., *Zh. Obshch. Khim.* 29, 2553 (1959a).
Bal'yan, Kh. V., and Borovikova, N. A., *Zh. Obshch. Khim.* 29, 2882 (1959b).
Batzer, H., and Weissenberger, G., *Makromol. Chem.* 12, 1 (1954).
Berkowitz, L. M., and Rylander, P. N., *J. Org. Chem.* 24, 708 (1959).
Blomquist, A. T., and Marvel, C. S., *J. Am. Chem. Soc.* 55, 1655 (1933).
Bond, G. C., "Catalysis by Metals," p. 303. Academic Press, New York, 1962.

Bond, G. C., Dowden, D. A., and Mackenzie, N., *Trans. Faraday Soc.* **54**, 1537 (1958).

Bond, G. C., Webb, G., Wells, P. B., and Winterbottom, J. B., *J. Catalysis* **1**, 74 (1962).

Bowers, A., Ringold, H. J., and Denot, E., *J. Am. Chem. Soc.* **80**, 6115 (1958).

Burwell, R. L., *Jr. Chem. Rev.* **57**, 895 (1957).

Burwell, R. L., Jr., and Hamilton, W., *Am. Chem. Soc. Div. Petrol Chem. Preprints* **4**, No. 2, A103 (1959).

Chase, G. O., and Galender, J., U.S. Patent 2,883,431, Apr. 21, 1959.

Cram, D. J., and Allinger, N. L., *J. Am. Chem. Soc.* **78**, 2518 (1956).

Crombie, L., *J. Chem. Soc.* p. 3510 (1955).

Crombie, L., and Harper, S. H., *J. Chem. Soc.* p. 2685 (1950).

Crombie, L., and Jacklin, A. G., *J. Chem. Soc.* p. 1622 (1957).

Csuros, Z., Geczy, I., and J. Polgar, *Acta Chim. Acad. Sci. Hung.* **1**, 417 (1951).

Dale, J., Hubert, A. J., and King, G. S. D., *J. Chem. Soc.* p. 73 (1963).

Dobson, N. A., Eglinton, G., Krishnamurti, M., Raphael, R. A., and Willis, R. G., *Tetrahedron* **16**, 16 (1961).

Easton, N. R., Dillard, R. D., Doran, W. J., Livezey, M., and Morrison, D. E., *J. Org. Chem.* **26**, 3772 (1961).

Ege, S. N., Wolovsky, R., and Gensler, W. J., *J. Am. Chem. Soc.* **83**, 3080 (1961).

Evans, R. J. D., Landor, S. R., and Smith, R. T., *J. Chem. Soc.* p. 1506 (1963).

Freidlin, L. Kh., and Kaup, Yu. Yu., *Dokl. Akad. Nauk SSSR* **152** (6), 1383 (1963).

Fukuda, T., and Kusama, T., *Bull. Chem. Soc. Japan* **31**, 339 (1958).

Gensler, W. J., Personal communication, 1963.

Gensler, W. J., and Schlein, H. N., *J. Am. Chem. Soc.* **77**, 4846 (1955).

Gensler, W. J., and Thomas, G. R., *J. Am. Chem. Soc.* **73**, 4601 (1951).

Ghera, E., Gibson, M., and Sondheimer, F., *J. Am. Chem. Soc.* **84**, 2953 (1962).

Hennion, G. F., and Barrett, S. O., *J. Am. Chem. Soc.* **79**, 2146 (1957).

Hennion, G. F., and Perrino, A. C., *J. Org. Chem.* **26**, 1073 (1961).

Hennion, G. F., Schroeder, W. A., Lu, R. P., and Scanlon, W. B., *J. Org. Chem.* **21**, 1142 (1956).

Hershberg, E. B., Oliveto, E. P., Gerold, C., and Johnson, L., *J. Am. Chem. Soc.* **73**, 5073 (1951).

Hort, E. V., U.S. Patent 2,953,604, Sept. 20, 1960.

Isler, O., Lindlar, H., Montavon, M., Rüegg, R., and Zeller, P., *Helv. Chim. Acta* **39**, 249 (1956).

Jacobson, M., Beroza, M., and Jones, W. A., *J. Am. Chem. Soc.* **83**, 4819 (1961).

Johnson, A. W., "The Chemistry of the Acetylenic Compounds," Vol. I, p. 91. Arnold, London, 1946.

Levinzon, A. L., *Sb. Nauchn. Tr. Lening. Inst. Tochnoi Mekhan. i Optiki Mat. Mekhan. Khim.* **24**, 109 (1957).

Lindlar, H., *Helv. Chim. Acta* **35**, 446 (1952).

Lindlar, H., U.S. Patent 2,681,938, June 22, 1954.

McCrae, W., *Tetrahedron* **20**, 1773 (1964).

McQuillin, F. J., and Ord, W. O., *J. Chem. Soc.* p. 2902 (1959).

Marvell, E. N., and Tashiro, J., *J. Org. Chem.* **30**, 3991 (1965).

Mondon, A., *Ann. Chem. Liebigs* **577**, 181 (1952).

Morrow, D. F., Butler, M. E., and Huang, E. C. Y., *J. Org. Chem.* **30**, 579 (1965).

Nazarov, 1. N., Rakcheeva, V. N., Raigorodskaya, V. Ya., and Azerbaev, 1. N., *Bull. Acad. Sci. URSS Classe Sci. Chim.* **305** (1946).

Newman, H., *J. Org. Chem.* **29**, 1461 (1964).

Nikitin, V. I., and Timofeeva, I. M., *Zh. Obshch. Khim.* **27**, 1814 (1957).

Nogaideli, A. I., and Vardosanidze, Ts. N., *Zh. Obshch. Khim.* **33**, 379 (1963).

Oroshnik, W., U.S. Patent 2,845,462, July 29, 1958.

Ott, E., and Schroter, R., *Chem. Ber.* **60B**, 624 (1927).

Plate, A. F., and Stanko, V. I., *Izv. Akad. Nauk SSSR Otd. Khim. Nauk* p. 1481 (1960).

Reppe, W., *et al.*, *Ann. Chem. Liebigs* **596**, 25 (1955).

Rieche, A., Grimm, A., and Albrecht, H., *Brennstoff-Chem.* **42**, 177 (1961).

Rylander, P. N., and Cohn, G., *Actes 2ᵉ Congr. Intern. Catalyse, Paris, 1960* p. 977. Editions Technip, Paris, 1960.

Rylander, P. N., and Himelstein, N., Unpublished observations, Engelhard Ind., 1964.

Schinz, H., *Kosmetik-Parfum-Drogen Rundschau* p. 1 (1955).

Seher, A., *Fette, Seifen, Anstrichmittel* **57**, 1031 (1955).

Shostakovskii, M. F., Bogdanova, A. V., and Krasil'nikova, G. K., *Izv. Akad. Nauk SSSR Otd. Khim. Nauk* p. 320 (1959).

Siegel, S., and Smith, G. V., *J. Am. Chem. Soc.* **82**, 6087 (1960).

Sokol'skii, D. V., "Hydrogenation in Solutions," Davey, New York, 1964.

Sokol'skii, D. V., and Dunina, L. P., *Dokl. Akad. Nauk SSSR* **132**, 1111 (1960).

Sondheimer, F., Wolovsky, R., and Amiel, Y., *J. Am. Chem. Soc.* **84**, 274 (1962).

Takei, S., and Ono, M., *Nippon Nogei Kagaku Kaishi* **18**, 625 (1942a).

Takei, S., and Ono, M., *Nippon Nogei Kagaku Kaishi* **18**, 119 (1942b).

Tedeschi, R. J., *J. Org. Chem.* **27**, 2398 (1962).

Tedeschi, R. J., and Clark, G., Jr., *J. Org. Chem.* **27**, 4323 (1962).

Zal'kind, Yu. S., and Boroda, T. A., *J. Gen. Chem. USSR (English Transl.)* **15**, 90 (1945).

Zal'kind, Yu. S., and Iremadze, I., *Zh. Obshch. Khim.* **18**, 1554 (1948).

Zal'kind, Yu. S., and Zhuravleva, L., *Zh. Obshch. Khim.* **18**, 984 (1948).

5

Olefins

The carbon–carbon double bond is very easily reduced. Successful reductions have been carried out over all the platinum metals in a variety of solvents and within a wide range of conditions. Only a few highly hindered olefins are resistant to hydrogenation. Olefins are the most popular of all substrates for mechanistic investigations and a vast amount of data has accumulated; Bond and Wells (1964) have given a good review of this aspect of olefin hydrogenation.

I. CATALYSTS

Several comparisons of platinum metals for hydrogenation of olefins have been made. The tendency of platinum metals to promote double-bond migration during hydrogenation of pentene-1 fell in the order, palladium $\gg$ ruthenium > rhodium > platinum $\gg$ iridium. Of particular interest was the observation that the results were mostly the property of the metal and relatively little affected by the support or the solvent. The sequence of selectivities for reduction of 1,3-pentadiene to monoolefin was palladium > rhodium > ruthenium $\simeq$ platinum > iridium. That is, palladium on half-hydrogenation of pentadiene gave the most pentene, iridium the least (Bond and Rank, 1965). These results for order of selectivity are probably applicable generally to simple diolefins, but not necessarily to those containing other functional groups.

Farmer and Galley (1933) have pointed out that selectivity in reduction of diolefins depends both on the substrate structure and on the age of the catalyst, where aging implies either a lapse of time or previous use. The effect of catalyst age was demonstrated in partial hydrogenation of sorbic acid, where new and aged (by use) platinum oxide catalysts gave quite different distributions of intermediate products. In our experience, aging by time has relatively little effect on the outcome of reduction, provided the

catalyst has been adequately protected from the atmosphere. Reuse, however, frequently changes the products of reduction. With reuse, catalyst activity diminishes (with some exceptions) at a gradual to fast rate, depending on the system. If a broad generality can be made, it is that selectivity increases as the catalyst is reused. Deliberate deactivation through additives and deactivation by use often produce quite similar results.

Palladium, platinum, and nickel catalysts were compared for relative ability to achieve preferential reduction of double bonds in methyl linolenate compared to methyl linoleate (selectivity), and for relative ability to cause isomerization of *cis* into *trans* isomers. The ratio of rates for these two reactions ranged for nickel catalysts at 140°C between 1.48 and 2.71; for palladium catalysts at 25°C between 1.68 and 1.99; and for platinum catalysts at 25°C between 1.33 and 1.61 (Johnston *et al.*, 1962). The hydrogenations were done in a system agitated by a magnetic stirring bar, so that probably the consequences inherent in maintaining a hydrogen-deficient catalyst are reflected in these ratios (Zajcew, 1960a). Platinum catalysts produced the lowest isomerization, but their selectivities were also low. Zajcew (1960b) had noted the same selectivity order for platinum and palladium in a study of linoleic-containing oils.

Zajcew (1960b) evaluated all the platinum metals-on-carbon except osmium for reduction of tall oil fatty acids. The activity of the metals increased in the order, ruthenium < iridium < platinum < rhodium < palladium. The tendency of these metals to promote *cis-trans* isomerization increased in the order, platinum < iridium ≃ ruthenium < rhodium ≃ palladium. The order of metals with regard to selectivity (preferential removal of greatest unsaturation was iridium < ruthenium < platinum < rhodium < palladium. Palladium catalysts were examined in more detail. As palladium was more highly dispersed on the carrier it became more active and more selective. At the expense of activity, selectivity was increased, and the *trans* isomers formed decreased by partial deactivation of the catalyst.

Other workers found a different order of activity of platinum metals for *cis-trans* isomerization of *cis*-stilbene in ethanol. At half-hydrogenation the amount of *trans*-stilbene in the product increased with the catalyst in the order, ruthenium < platinum ≪ palladium ≪ rhodium. Ruthenium, unique among the metals, gave the same degree of isomerization with or without hydrogen present (Bellinzona and Bettinetti, 1960). The rate of *cis-trans* isomerization relative to the rate of hydrogenation may depend on the amount of catalyst and on the initial isomer. With very small amounts of palladium-on-carbon, *cis*-undec-4-ene was transformed rapidly in the presence of hydrogen to a mixture containing about 70% of the *trans* isomer. Under the same conditions *trans*-undec-4-ene was rapidly reduced. The authors pointed out that the results indicate the pure *trans* isomer to undergo hydrogenation more readily than the *cis*, and furthermore that, in a mixture

of the two, the *cis* isomer preferentially occupies the hydrogenation sites and inhibits hydrogenation of the *trans* isomer (Dobson *et al.*, 1961).

CHOICE OF CATALYST

Most catalytic reductions of olefins are carried out over palladium or platinum. Both metals make extremely active catalysts for this purpose and usually give excellent results. Preference for one or the other is determined largely by other functions in the molecule, and in polyolefins by considerations of selectivity. The literature indicates that platinum gives generally more extensive hydrogenation, but this may stem from the unequal amounts of metal used in most comparisons of supported palladium and unsupported platinum. For instance, vinylcyclooctatetraene absorbed five equivalents of hydrogen over platinum oxide in acetic acid, 4.5 equivalents over platinum oxide in methanol, and only 4.0 equivalents over 10% palladium-on-calcium carbonate (Larrabee and Craig, 1951). The converse situation is also found, and in phenyl-substituted ethylenes the effect is pronounced. With platinum, each additional phenyl group causes a decrease in rate of hydrogenation and tetraphenylethylene is not reduced at all. With palladium, the retarding effect of the phenyl group becomes evident only in the slow hydrogenation of tetraphenylethylene (Yurashevskii, 1938). This example points up one of the difficulties in correlating rate of hydrogenation with structure; that is, the relative rates of hydrogenation of various substrates depend on the catalyst as well as the structure of the substrate.

Palladium-on-calcium carbonate and platinum oxide were quite different in reduction of I in ethyl acetate. The palladium-catalyzed reduction practically ceased after absorption of one equivalent of hydrogen and afforded an 85% yield of the dihydro adduct (II). On the other hand, over platinum oxide the reduction continued and gave a mixture of tetrahydro derivative (III) and hexahydro derivative (IV) with a structure presumably as shown.
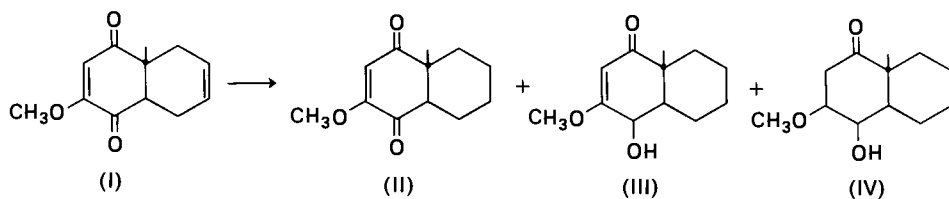
The authors pointed out that, of the two carbonyl groups in the adduct, one is much less susceptible to reduction than the other. They attributed this behavior to the interaction of the unreactive carbonyl with the methoxy function through the double bond (Woodward *et al.*, 1952),
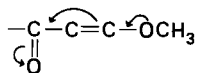
The relative merits of platinum oxide, palladium oxide, palladium-on-carbon, and palladium-on-barium sulfate in ethanol, acetic acid, and ethyl acetate were evaluated for selective reduction of the exocyclic double bond in a series of unsaturated 2-imidazolin-5-ones. Platinum oxide or palladium-on-strontium carbonate in ethyl acetate provided the best conditions (Kidwai and Devasia, 1962).
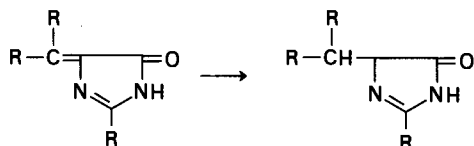
1. Iridium, Rhodium, and Ruthenium

These metals have been little used for hydrogenation of olefins, but some very satisfactory results have been obtained. They seem most useful when a selectivity problem is involved.

Iridium catalysts are claimed to be especially useful in stereospecific hydrogenation of 17α-hydroxy-20-keto-16-methylene steroids of the pregnane series to the corresponding β-methyl derivatives. Examples were given with 5% iridium-on-barium sulfate in ethanol or ethyl acetate, 5% iridium-on-kieselguhr in ethanol, iridium dioxide in ethanol, and 7.5% iridium-on-calcium carbonate in ethyl acetate. In some cases the yield of β-isomer was so high that the need for any purification step was eliminated (Phillipps, 1963; Gregory et al., 1966).

Rhodium has proved quite useful in hydrogenation of olefins, when concomitant hydrogenolysis of an oxygen function was to be avoided (Bonner et al., 1964). An example where the oxygen function is an epoxide was cited by Tarbell et al., (1961). Rhodium-on-alumina was found to be a superior catalyst for hydrogenation of vinylic or allylic halogen-substituted olefins to haloalkanes. Yields of 40–60% were obtained from hydrogenation of 1-chloropropene, allyl chloride, and 1,3-dichloropropene. The yields of dichloropropane from hydrogenation of 1,3-dichloropropene at 100° and 400–600 psig were 47.9%, 19.2%, and 6.1% when carried out over 5% rhodium-, 5% palladium-, and 5% platinum-on-alumina, respectively. Alumina proved to be a more effective support for rhodium than did carbon; the yields of dichloropropane were 47.9% and 37.4%. The solvent had marked effect on the yield of dichloropropane. With 5% rhodium-on-alumina the yields of dichloropropane obtained at 100°C and 400–600 psig were with cyclohexane, 1,3-dichloropropane, diethyl ether, ethanol, and acetic acid as solvents, 47.9%, 39.4%, 30.8%, 2.5%, and 2.5% respectively (Ham and Coker, 1964). The results on solvent effect found here agreed with other work, in that the less polar solvents gave the least hydrogenolysis. However, unlike

the earlier work (Kindler *et al.*, 1953), the use of catalyst inhibitors, such as thiophene, had an adverse effect on the yield.

Rhodium-on-alumina proved to be an excellent catalyst for reduction of vinylene carbonate to ethylene carbonate (Newman and Addor, 1955). This catalyst worked very well while all others tested failed in one way or another to give the desired product (Addor, 1964). A selective reduction of the unsaturated ketonic lactone (V) was achieved over 5% rhodium-on-carbon in ethyl acetate. The double bond conjugated with the ketone function was reduced rapidly (VI). Further hydrogenation resulted in saturation of both double bonds (VII). Reduction over rhodium gave a 95% yield of the dihydrolactone; over palladium-on-carbon only 40% of crude material was obtained, and the product was contaminated by an acid presumably arising through hydrogenolysis of the lactone (Roy and Wheeler, 1963).

(VII)   (V)   (VI)
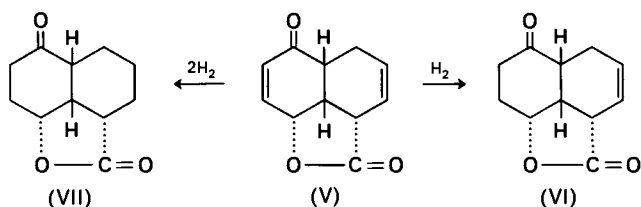
Rhodium proved much superior to palladium or platinum in selective hydrogenation of the olefinic function of toxol (VIII). Hydrogenation of toxol over palladium or platinum resulted in extensive hydrogenolysis and a complex product mixture, but over 5% rhodium-on-alumina in 95% ethanol the reduction ceased after absorption of one equivalent of hydrogen, smoothly affording dihydrotoxol (IX). Further reduction of dihydrotoxol over 10% palladium-on-carbon in ethanol gave dihydrotremetone (X) (Bonner *et al.*, 1964).

(VIII)   (IX)   (X)
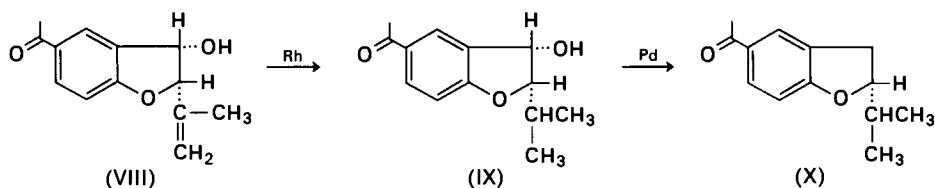
Rhodium has also been used to achieve highly stereoselective reductions. Hydrogenation of XI over 5% rhodium-on-alumina in acetic acid gave XII.

(XI)   (XII)
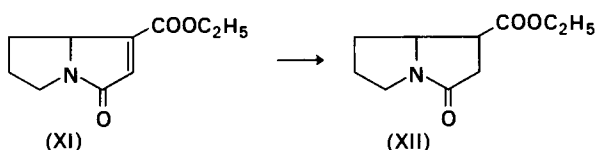
The catalyst and hydrogen approached the less hindered side of the pyr-rolizidine nucleus, thus pushing the carbethoxy function to the inside of the fold (Nair and Adams, 1961).

Similarly, a highly stereoselective reduction of 1,3-cyclopentan-1-enedipropionic acid over 5% rhodium-on-alumina in acetic acid gave pure *cis*-dipropionic acid in 86% yield. The stereoselectivity obtained in this reduction was an aid in assigning the structure of the substrate (Westman and Kober, 1964).

Ruthenium has been used for selective saturation of conjugated dienes. Hydrogenation of 19.5 gm XIII in 530 ml methanol over 4 gm 5% ruthenium-on-carbon at room temperature and 40 psig afforded XIV in 71% yield after recrystallization (Hasek *et al.*, 1964).

(XIII)   (XIV)
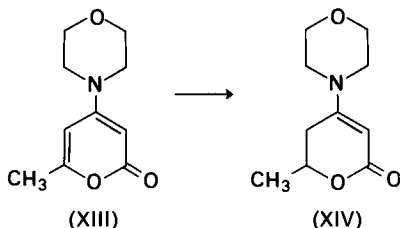
Ruthenium catalysts were remarkably selective in hydrogenation of mixtures of olefins. Monosubstituted olefins were reduced preferentially in the presence of di- and trisubstituted olefins. For instance, in a mixture of 2-octene and 1-octene the terminal olefin was completely reduced before any of the 2-octene was saturated. Selectivity of this type is possible because double-bond migration is relatively slow over ruthenium; over palladium, 1-octene had substantially disappeared through isomerization when hydrogenation was only 10% complete. All reductions of these mixtures of olefins over ruthenium were carried out in the presence of water; without water the hydrogenation proceeded very slowly if at all (Berkowitz and Rylander, 1959).

Ruthenium has made a useful catalyst for hydrogenation of allylic oxygen compounds, when hydrogenolysis was to be avoided (Cope *et al.*, 1957). Ruthenium dioxide was the catalyst of choice for hydrogenation of the tetrasubstituted double bond in guaiol (XV), a compound known to be reduced with difficulty (Plattner and Lemay, 1940; Plattner and Magyar,

(XV)   (XVI)
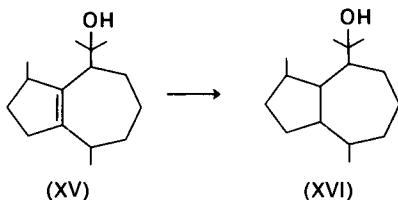
1942). Reduction of this compound is complicated by the tendency of the tertiary hydroxyl to undergo hydrogenolysis and by formation of a mixture of isomers. Ruthenium dioxide at 1500 psig provided the largest quantity of dextrorotatory dihydroguaiol (XVI) (Eisenbraun *et al.*, 1960).

2. *Amount of Catalyst*

The reduction of cinnamaldehyde provides an interesting example of the complex and sensitive relationship sometimes found between the amount of catalyst and the reaction products. Cinnamaldehyde was reduced over various amounts of colloidal palladium and the product analyzed after exactly one equivalent of hydrogen had been absorbed. Some results, taken from a graph, are shown in Table I. A high percentage of double bond reduction corresponds closely to a high yield of hydrocinnamaldehyde, and a low

TABLE I

HYDROGENATION OF CINNAMALDEHYDE OVER COLLOIDAL PALLADIUM[a]

Percent carbon–carbon bond hydrogenated	Pd solution (ml)
96	2
89	8
68	10
30	11
18	12
40	13
88	14

[a] Each reduction was stopped after absorption of one mole of hydrogen and the product analyzed.

percentage to a high yield of cinnamyl alcohol. The products formed depended critically on the amount of catalyst used. Good yields of cinnamyl alcohol could be obtained only over a very restricted range. The authors pointed out that this type of dependency can occur only when the rates of hydrogenation of the two groups are similar. A plot of the measured overall rate versus the amount of catalyst was unusual and showed both a maximum and a minimum. A plot of the rate of hydrogenation of the functions separately (derived from analysis of the product) gave curves similar in shape to that of the overall rate curve (Csuros, 1951).

The stereochemistry of reduction may also be changed by the amount of catalyst used (discussed in Section V).

3. Diene Hydrogenation

In general, palladium seems the most useful of the platinum metals for selective hydrogenation of diolefins whether conjugated or not, except when the diene is a potential aromatic system. The ability of platinum metals to selectivity remove nonconjugated multiple unsaturation in a mixture of natural fatty oils increased in the order, iridium < ruthenium < platinum < rhodium < palladium (Zajcew, 1960b). Palladium was also the most selective catalyst in hydrogenation of 1,3-pentadiene (Bond and Rank, 1965) and 1,4-pentadiene (Freidlin *et al.*, 1965). Palladium was much more selective than platinum in partial hydrogenation of a series of conjugated aliphatic dienes (Kanzanskii *et al.*, 1958). Palladium-on-alumina was completely selective for hydrogenation of 1,3-butadiene to butene; whereas other metals gave some butane as an initial product, and butane was the major product of iridium-catalyzed reductions (Bond *et al.*, 1965). High yields of butenes were obtained by partial hydrogenation of butadiene over palladium catalysts at $-12°C$ (Young *et al.*, 1947). Palladium-on-alumina proved to be a very satisfactory catalyst for selective, continuous hydrogenation of diolefins, mainly cyclopentadiene, in dripolene (Keith and Rylander, 1965). Palladium black selectively reduced cyclopentadiene to cyclopentene, whereas platinum black and platinum-on-barium sulfate were nonselective (Freidlin and Polkovnikov, 1957). Supported palladium is the preferred catalyst for selective hydrogenation of cyclododecatriene at 130–180°C to cyclododecene (Belgian Patent 654,990). Palladium chloride in water has been used for the same reduction (Belgian Patent 664,906). The symmetrical diolefin, 1,5-cyclooctadiene, was selectively reduced over 5% palladium-on-calcium carbonate in methanol to *cis*-cyclooctene, isolated in 87% yield.* The rate of this reduction over palladium catalysts decreases sharply after the first mole of hydrogen has been absorbed. Cyclooctene is known to be reduced with unusual slowness (Jardine and McQuillin, 1966). The ratio of the rates of absorption of the first and second moles of hydrogen depends on the method of preparation of the catalyst, on the carrier, and on various additives. Two moles of hydrogen are absorbed over rhodium-on-carbon at a fast and constant rate, making this the catalyst of choice for complete saturation (Rylander and Karpenko, 1961).

Palladium may not be the best catalyst for hydrogenation of dienes contained in potential aromatic systems. Attempts to hydrogenate such systems may lead through disproportionation to a paraffin and an aromatic, the latter being relatively difficult to reduce. The double bonds of 1,3-cyclo hexadiene were reduced in heptane over palladium or platinum black with intermediate formation of cyclohexene. The accompanying disproportiona-

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* The heat of reaction was conveniently dissipated by wrapping the bottle with a towel and periodically saturating it with acetone (Gardner and Narayana, 1961).

tion-reduction to benzene and cyclohexane was favored by palladium, whereas platinum promoted the hydrogenation (Freidlin *et al.,* 1959). Rosin acids are difficult to saturate because of a tendency under hydrogenation conditions to undergo this type of disproportionation (Montgomery *et al.,* 1958).

II. EFFECT OF SOLVENT

The rate, selectivity, and stereochemistry of reduction of olefins may each be profoundly affected by the solvent. The rate of reduction of olefins over palladium-on-carbon in ethanol was considerably retarded by alkali, but the rate of olefin saturation in α,β-unsaturated ketones was virtually unchanged (McQuillin and Ord, 1959). The influence of alkali on the relative rates of reduction of different types of olefin was put to excellent use in achieving a selective reduction of the trienone, 4,6,22-ergostatriene-3-one, to the 4,22-dienone.
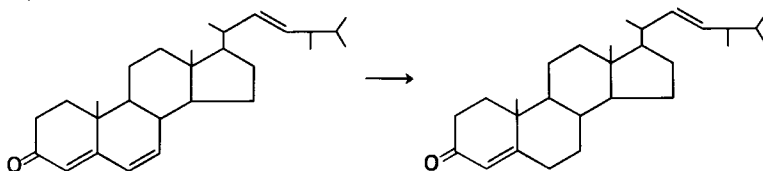
A fair selectivity was obtained over palladium-on-carbon in a variety of solvents. Optimum selectivity was found in alcoholic sodium or potassium hydroxide solution of circumscribed concentration. Uniformly high conversions were obtained in 0.001–0.01 N potassium hydroxide, but above and below this concentration the yields fell. Prereduction of the catalyst was also necessary for optimum selectivity. Under these conditions the dienone could be isolated in yields of 70–75 %. The authors believe the increased selectivity observed in basic media to be caused by base-catalyzed enolization of the various ketonic reactants, and differences between the enolates in regard to rate of adsorption, reduction, and desorption to be greater than between the corresponding ketones (Shepherd *et al.,* 1955). A detailed kinetic study of this hydrogenation has been made (Garrett *et al.,* 1956). Alkaline media are frequently employed in hydrogenation of α,β-ketones (further examples are given in the section on stereochemistry).

Selectivity may be affected markedly by the polarity of the solvent. The dienone (XVII) could be hydrogenated over palladium-on-carbon in the presence of a small amount of alkali to either cholestan-7-one (XVIII) or Δ^5-cholesten-7-one (XIX), depending on the solvent.
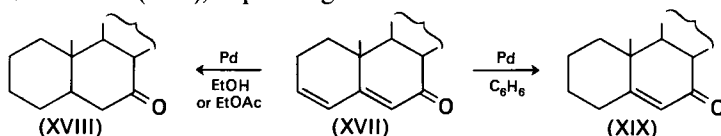
Hydrogenation of 6 gm XVII in 342 ml benzene, 137 ml ethanol, and 1 ml 15% aqueous potassium hydroxide over 0.96 gm 5% palladium-on-carbon ceased spontaneously after 1.1 moles of hydrogen had been absorbed. The work-up, which included an isomerization step to convert any non-conjugated olefin to XIX, afforded XIX in 77% yield. Hydrogenation of XVII in ethanol or ethyl acetate containing potassium hydroxide over 5% palladium-on-carbon ceased after absorption of two moles of hydrogen and afforded XVIII in 78% yield (Nickon and Bagli, 1961).

The dependence on solvent observed with XVII is reminiscent of the behavior of the dienone system (XX), in which reductions over palladium in polar solvents absorbed two moles of hydrogen and produced a complicated mixture of products, whereas in benzene only one more of hydrogen was absorbed and excellent yields of XXI were obtained. The authors thought that the results obtained in polar solvent, particularly facile saturation of a tetrasubstituted double bond, implicated the carbonyl function in the reduction, and reasoned that in nonpolar solvents participation of the carbonyl group would be suppressed (Woodward et al., 1952).

(XX) → (XXI)
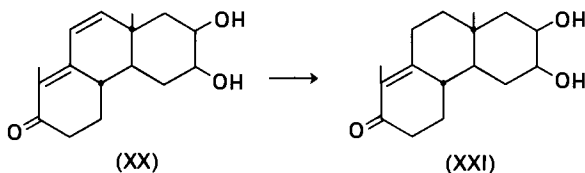
STRONG ACIDS

Traces of strong acids may prove powerful catalysts in reduction of olefins resistant to hydrogenation. For instance, hydrogenation of epi-cholesterol did not proceed over platinum oxide in methanol containing acetic acid, but hydrogen bromide, perchloric acid, or sulfuric acid all served as promoters (Lewis and Shoppee, 1955). The strong acids—sulfuric, maleic, oxalic, phosphoric, hydrochloric, p-toluenesulfonic, citric, and perchloric, all with pK lower than 3, were effective promoters in hydrogenation of cholesterol over platinum oxide. Of these acids, the authors noted that perchloric, sulfuric, p-toluenesulfuric, hydrochloric, and oxalic acids were known to form addition products with cholesterol. By use of perchloric acid as a promoter, ethyl acetate instead of acetic acid could be used as a solvent with the advantage that very little cholestanyl acetate was formed (Hershberg et al., 1951). In the presence of perchloric acid some reduction of the acetic acid solvent may occur also (Chanley and Mezzetti, 1964).

Strong acids may interact also with the catalyst. $\Delta^{9,10}$-Octalin was reduced at a negligible rate over platinum oxide unless acetic acid was added or the

catalyst was prereduced in dilute acid. In some experiments low hydrogena-
tion rates were obtained because of severe clumping of the catalyst. Clumping
during hydrogenation could be prevented in large measure by an acetone
wash of the prereduced catalyst and mechanical disintegration of the catalyst
with a stirring rod, followed by several washings with hexane. Catalysts so
treated suspended reasonably well (Smith and Burwell, 1962). [Other effects
of acid on platinum oxide catalysts are discussed in Chapter 25 (Dart and
Henbest, 1960).]

III. EFFECT OF OLEFIN STRUCTURE

Many studies correlating structure with rate of hydrogenation have been
made (Corson, 1955). The broadest, generally useful guide to emerge is that
the rate of hydrogenation of a double bond decreases as the number and
bulk of the substituents in the vicinity of this function increase. From this it
follows that, in competitive hydrogenation of a mixture of olefins or a single
molecule containing several olefinic functions, the least hindered olefin
will be preferentially reduced. When, as sometimes happens, this fails to be
the case, recourse may be had to various arguments—that the steric effect
was misjudged, another functional group intervened, isomerization occurred,
or the molecule was solvated. Nonetheless, for an a priori assessment of the
possibility of selective hydrogenation and of the direction it will take, the
above generality is useful.

A. TETRASUBSTITUTED OLEFINS

Tetrasubstituted olefins are reduced with some difficulty and survive
many reductions even though no effort is made to limit absorption (Over-
berger and Kabasakalian, 1957). Reduction of 1,2-dimethylcyclooctatetraene
over 1 % palladium-on-calcium carbonate in methanol stopped spontaneous-
ly after absorption of three equivalents of hydrogen. The remaining tetra-
substituted double bond was saturated over platinum oxide in acetic acid
(Cope and Campbell, 1952):
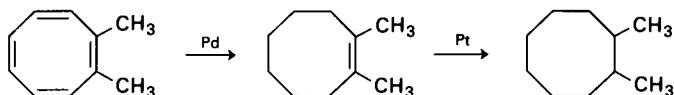
These results suggest that platinum is a more potent catalyst than palladium
for reducing hindered double bonds. However, roughly 60 times as much
platinum as palladium per weight of substrate was used. If very large amounts
of metal are needed in a reduction, the use of a nonsupported catalyst may
facilitate recovery of the product.

The presence of a tetrasubstituted double bond in genipic acid (XXII) was inferred from its failure to absorb hydrogen over 5% palladium-on-carbon in ethanol. However, when prereduced platinum oxide was used, the substrate absorbed one equivalent of hydrogen. Among the products isolated was the lactonic acid (XXIII), postulated to have arisen by migration of the double bond (Tallent, 1964). Again, these comparisons do not necessarily infer that platinum is a more potent catalyst than palladium for reduction of a tetrasubstituted double bond; about twenty times more platinum than palladium was used. Perhaps the inference to be drawn is that highly hindered double bonds can be hydrogenated if sufficient catalyst is used.

(XXII)   (XXIII)
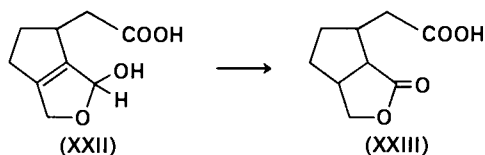
B. STRAINED BONDS

It appears that hydrogenation of a double bond is facilitated by steric strain. For instance, although tetrasubstituted olefins are usually resistant to hydrogenation, isolanostadiene readily absorbed 1.8 moles of hydrogen. The author suggested this unusual reactivity of the normally inert 8,9 double bond to be attributable to the steric strain introduced into the B ring of the lanostane skeleton by the *trans* fusion of the five-membered A ring (Huffman, 1959). Inasmuch as double-bond migration may have preceded hydrogenation, no stereochemical relationships were implied.

Another example indicating preference for hydrogenation of strained olefins is the reduction of the potassium salt of the diolefin (XXIV) obtained from maleic anhydride and cyclooctatetraene. Hydrogenation proceeded stepwise over 10% palladium-on-carbon in water; the double bond in the strained four-membered ring was reduced first (Cope *et al.*, 1952).

(XXIV)
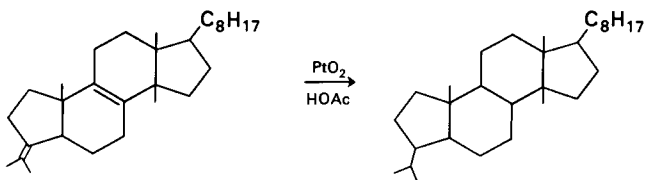
The photoisomer of isocolchicine (XXV) rapidly absorbed one mole of hydrogen over platinum oxide in ethanol with saturation of the strained ring (Chapman *et al.*, 1963). A model of this compound provided no reason, based on considerations of steric hindrance to the approach of the catalyst, for this result; both centers of unsaturation appeared to be equally accessible to the catalyst.
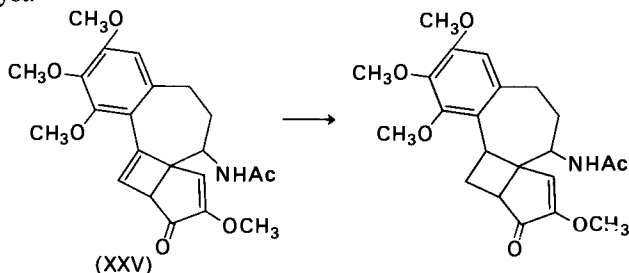
Similarly, the more strained internal double bond of 5-methylenebornene was reduced in preference to the methylene group; after absorption of one equivalent of hydrogen the product was essentially methylenenorbornane (Cristol *et al.*, 1965).
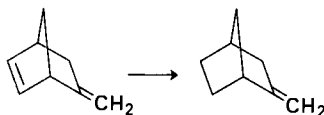
C. SELECTIVE REDUCTION OF DIOLEFINS

In general, the less hindered double bond in a diolefin is preferentially hydrogenated. Reduction of limonene over 5% palladium-on-carbon without solvent virtually stopped after complete removal of the disubstituted olefin, and Δ^1-p-menthane was obtained in practically quantitative yield (Newhall, 1958):
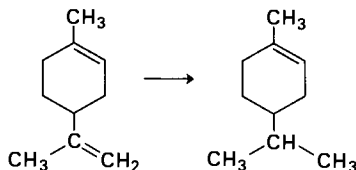
The author pointed out that it is imperative to use only freshly distilled material, as the catalyst was rapidly poisoned by limonene stored in contact with air for as little as 5 days. The same catalyst was used for as many as thirty hydrogenations, and spent catalyst was easily reactivated by washing with acetone and drying for 1 hour at 110°C. Selective reduction of limonene was achieved long ago by Vavon (1911), using a platinum black catalyst;

the reduction proceeded stepwise and continued until 2 moles of hydrogen had been absorbed. Limonene has also been selectively reduced over platinum oxide in methanol (Fujita and Matsuura, 1955). Impurities in limonene were shown, in one series of experiments using platinum oxide, to affect the rate of hydrogenation of the second double bond more than the rate of the first. Before purification, the time required for absorption of the first and second moles of hydrogen was 5 minutes and 138 minutes; after purification, the respective times were 4 minutes and 15 minutes (Kern *et al.*, 1925). From a study of the reduction of several terpenes over platinum oxide, the generality was made that exocyclic double bonds are reduced more easily than those in the ring (Smith *et al.*, 1949). Hydrogenation of 4-vinylcyclohexene afforded only 4-ethylcyclohexene (Tepenitsyna *et al.*, 1963).

The above results contrast with the complete lack of selectivity observed in hydrogenation of an isomeric diene, 1(7),8-*p*-menthadiene, in which both double bonds are disubstituted. After absorption of one mole of hydrogen no monoolefin could be detected in the product, which consisted of about 50% unchanged starting material and 25% each of *cis*- and *trans-p*-methane (Webb and Bain, 1953). One might guess that palladium would have offered more chance of a selective partial hydrogenation.
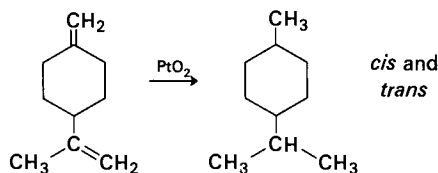
Various factors may work to invalidate the simple generality that the less hindered olefin is reduced preferentially. Reduction of XXVI over 10% palladium-on-calcium carbonate afforded XXVII in 67–69% yield and XXVIII in 30% yield, the major product being derived by reduction of the more hindered olefin:
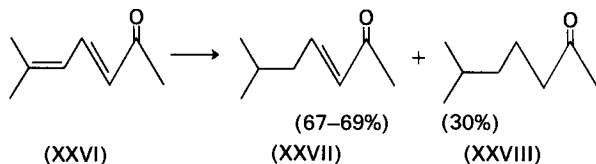
When the corresponding alcohol (XXIX) was similarly reduced, the product distribution after absorption of 0.82 mole of hydrogen was 3.7% XXX, 63.3% XXXI, and 33% XXXII and XXXIII together. The results suggest that the more hindered double bond in XXVI was reduced preferentially through participation of the carbonyl by 1,6-addition (Miropol'skaya *et al.*, 1962).
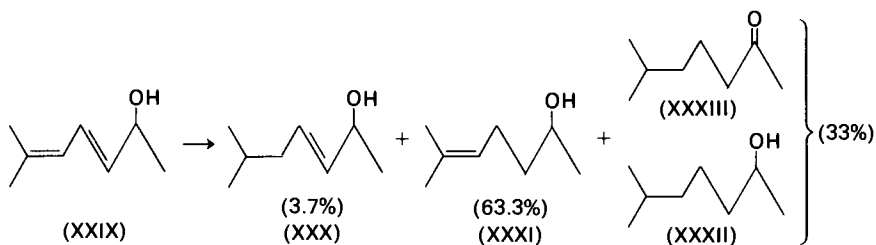
Hydrogenation of methyl and ethyl esters of XXXIV and XXXV, over 5% palladium-on-carbon, proceeded in such a manner as to implicate the ester group in the olefin saturation. On reduction, XXXIV rapidly absorbed three moles of hydrogen, saturating all but the least substituted bond (a). The fourth mole was absorbed very slowly, producing the cyclooctane in quantitative yield. On the other hand, hydrogenation of XXXV rapidly produced the corresponding cyclooctane; no intermediate cyclooctene could be isolated (Leto and Leto, 1961).
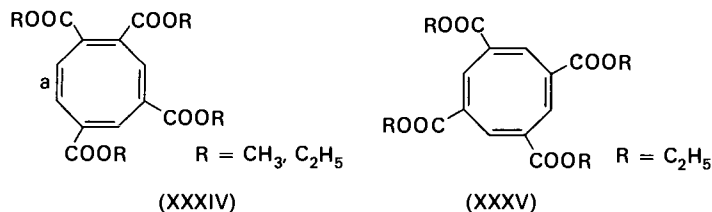
Selective reduction of diolefins may be influenced by substituents, remote from either center of unsaturation, which control the orientation of the substrate on the catalyst. Reduction of the dienone (XXXVI) over 5% palladium-on-carbon was essentially nonselective. Nor was much selectivity observed in reduction of the endo alcohol (XXXVII). On the other hand, high yields of a single product were obtained in reduction of the *endo*-acetate (XXXVIII) and *endo*-tosylate (XXXIX). These results were surprising, for it might have been expected that the bulky substituents would impede

(XXXVI) R = =O	70	30
(XXXVII) R = —OH	60	40
(XXXVIII) R = Acetate	95	5
(XXXIX) R = Tosylate	>95	—
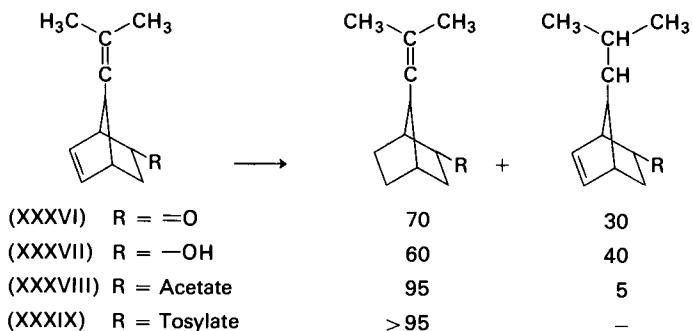
reduction of the endocyclic double bond. The authors believe that the substituents serve as points of adsorption on the catalyst surface, and consequently control the manner in which the diene is attached to this surface. Very low amounts of catalyst were used in this work; when the amount of catalyst was increased the reduction was more random (DePuy and Story, 1960).

Allenes

Allenes are reduced in two distinct stages. Olefins and alkanes are produced in the first stage, in the second stage the olefin is saturated. The selectivity of reduction varies appreciably with the metal, and for allene itself at various temperatures decreased in the series, palladium > rhodium $\gtrsim$ platinum > ruthenium > osmium $\gg$ iridium (Bond and Wells, 1964). Allenes with terminal double bonds are selectively reduced in the terminal position; internal allenes afford a mixture of olefins (Bal'yan *et al.*, 1960). Hydrogenation of buta-2,3-dienoic acid over 1.5% palladium-on-calcium carbonate in ethyl acetate afforded *cis*-crotonic acid (Eglinton *et al.*, 1954). Hydrogenation of cumulenes over palladium–lead-on-calcium carbonate (Lindlar, 1952) affords *cis* polyenes (Kuhn and Fischer, 1960). Reduction of 500 mg XL over 800 mg Lindlar catalyst in 500 ml tetrahydrofuran gave XLI in 84% yield.

$$\phi_2C{=}C{=}C{=}C\phi_2 \longrightarrow \phi_2C{=}CH{-}CH{=}C\phi_2$$

$$\text{(XL)} \qquad\qquad \text{(XLI)}$$
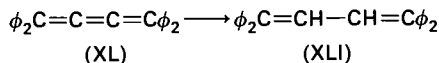
One mole of hydrogen was rapidly absorbed in reduction of 7 gm 1,2-cyclononadiene in 200 ml methanol over 10% palladium-on-carbon, affording *cis*-cyclononene in 76% yield after distillation. An abrupt decline in rate occurred after absorption of the first mole (Gardner and Narayana, 1961). The *cis* isomer is not necessarily the primary product of allene hydrogenation, for the *trans* olefin is rapidly isomerized under the reaction conditions. Hydrogenation of 1,2-cyclononadiene and 1,2-cyclodecadiene in methanol over 10% palladium-on-carbon produced initially 17% and 32% of the corresponding *trans* olefin (Moore, 1962).

IV. DOUBLE-BOND MIGRATION

Double-bond migrations during hydrogenation are probably very common but, unless tracers are used (Cookson *et al.*, 1962) or special products result or the new bond is resistant to hydrogenation, no evidence for the migration remains on completion of the reduction. Some understanding of the factors affecting isomerization has been acquired by measuring the extent of racemization in the products of hydrogenation of optically active

olefins. Reduction of (−)-3,7-dimethyl-1-octene over platinum oxide resulted in only 3% racemization, but over varying amounts of palladium-on-carbon, the product was 43–52% racemized. Racemization and therefore by inference isomerization were decreased by pressure, by inhibited catalysts, and by base. Reduction at 1500 psig over palladium-on-carbon gave only 23% racemized product, over a Lindlar catalyst at 1 atm gave 16%, and over palladium-on-carbon in the presence of small quantities of potassium hydroxide or pyridine gave 12% and 18%, respectively. The authors suggested that certain sites on the catalyst surface show enhanced activity for hydrogen addition, but particularly for double-bond migration; it is these sites that are largely deactivated by base and also perhaps by lead ions in the Lindlar catalyst (Huntsman *et al.*, 1963). Other workers (Bonner *et al.*, 1958), using tracer technique, have ruled out double-bond migration as the path by which optically active 3-phenyl-1-butene was racemized during hydrogenation (Cram, 1952). Bond and Wells (1964) have offered a mechanistic view of double-bond migration. Platinum metals vary widely in ability to promote double-bond migration; palladium is by far the most effective catalyst and should not be used when isomerization is to be avoided. The order of isomerization activity adduced for pentene-1 was palladium ≫ ruthenium > rhodium > platinum ≫ iridium (Bond and Rank, 1965). Presumably this order should be maintained for olefins generally. Hydrogenation of olefins over platinum oxide in acetic acid has been shown to be highly stereoselective in introducing both hydrogens from the same side of the molecule and to cause little if any isomerization (Siegel and Smith, 1960a; Sauvage *et al.*, 1961; Kaye and Matthews, 1964). In hydrogenation of certain cyclohexenes, isomerization increased with the catalyst in the order, platinum oxide < platinum-on-alumina < palladium-on-alumina (Siegel and Dmuchovsky, 1962).

The extent of isomerization depends importantly on the substrate, and certain conditions must be met for double-bond migrations to occur (Bream *et al.*, 1957). The allylic hydrogen to be removed must be sterically accessible to the catalyst and on the same side of the molecule as the entering hydrogen. Carboxyl groups conjugated to double bonds seem to reduce greatly the extent of double-bond migration (Smith and Roth, 1965). Reduction of the isomeric compounds dimethylitaconate (XLII), dimethylmesaconate (XLIII), and dimethylcitraconate (XLIV) was achieved with virtually no *cis-trans* isomerization or double-bond migration. Some striking results were obtained when these compounds were reduced with deuterium. Little deuterium ended up in the tertiary position of the resulting dimethylsuccinate when XLII or XLIII was the substrate, but a large amount of deuterium ended up in this position when XLIV was reduced. The authors point out that only in XLIV is there no olefinic hydrogen *cis* to a carbomethoxy, and postulate involvement of an enol-type species to account for the observed results. Each of the

substrates was reduced over platinum oxide, 5% palladium-on-carbon, and 5% rhodium-on-carbon. Distribution of deuterium in the resulting succinate depended much more on the substrate than on the catalyst.
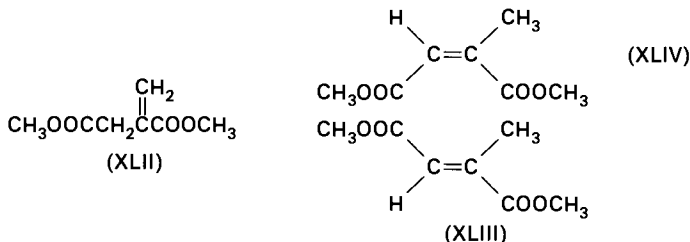
A. TETRASUBSTITUTED OLEFINS

A frequent consequence of double-bond migration is that a tetrasubstituted olefin results, which can be reduced only with difficulty. Reduction of XLV over 5% palladium-on-barium sulfate in ethanol afforded XLVI. The rapid reduction ceased after absorption of two moles of hydrogen (Rapoport et al., 1955).
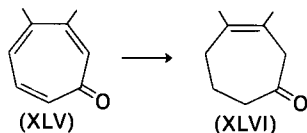
The amount of tetrasubstituted olefin formed may depend on the catalyst. Reduction of pulchellin (XLVII) over prereduced platinum oxide in ethanol gave dihydropulchellin (XLVIII). On the other hand, reduction of XLVII over palladium-on-carbon or palladium-on-calcium carbonate afforded XLVIII in 60–80% yield accompanied by the isomerized product, isopulchel- lin (XLIX). These results are in keeping with the greater tendency of palladium to cause double-bond migration. The relative amounts of these products is said to depend also on the experimental conditions (unspecified) (He z et al., 1963).
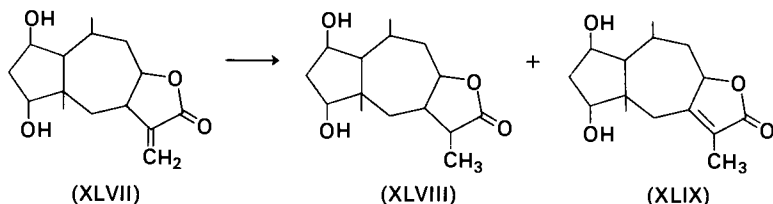
The effect of catalyst is more pronounced in hydrogenation of L. Over platinum oxide in acetic acid–ethyl acetate, 8(14)-ergostene (LI) resulted; over Raney nickel in benzene, 7,9(11)-ergostadiene was formed by 1,2- addition and without bond migration (Nes, 1956).
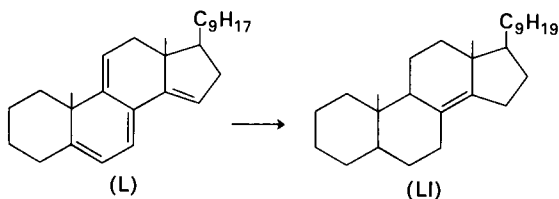
Attempted hydrogenation of the exocyclic double bond of hysterin over platinum oxide resulted in isomerization to isohysterin, which was resistant to hydrogenation, but reduction of hysterin was readily achieved over ruthenium dioxide at elevated temperatures and pressures (deVivar *et al.*, 1966). Other examples of double-bond migration to a tetrasubstituted position are found in hydrogenation of estafiatone over platinum oxide in acetic acid (Sanchez-Viesca and Romo, 1963), of flexuosin A over platinum oxide in acetic acid (Herz *et al.*, 1964), of azepine esters over platinum in cyclohexane (Anderson and Johnson, 1964), of multiflorenol over platinum oxide in acetic acid (Sengupta and Khastgir, 1963), of butyrospermol over platinum (Dawson *et al.*, 1955), and of methyl dihydromasticadienolate acetate over platinum oxide in deuteroacetic acid (Barton and Seoane, 1956). The last isomerization, carried out with deuterium, was used cleverly to deduce, from the position of the entering deuterium, the position of the double bond before migration.

B. Aromatization

Aromatization may provide a driving force for double-bond migration. For instance, reduction of 2,6-dimethyl-7,7-dicyanoquinonemethide over 5% palladium-on-carbon in benzene gave a 96% yield of the corresponding phenol (Takimoto *et al.*, 1964):
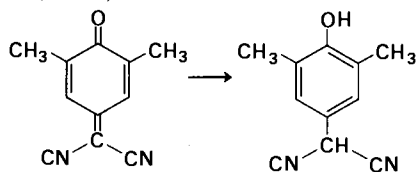
Aromatization and isomerization accompanied hydrogenation over platinum oxide in acetic acid of the conjugated polyolefin, hortiamine, to dihydrohortiamine (Pachter *et al.*, 1960):
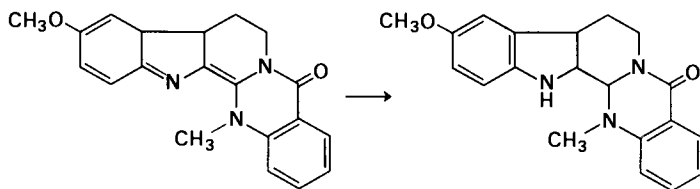
Aromatic systems may be formed during hydrogenation of olefins through disproportionation. For instance, catalytic hydrogenation of ligustilide (LII) over palladium-on-barium sulfate affords a mixture of dihydro- (LIII) and tetrahydroligustilide (LIV), and 3-butyl phthalide (LV) (Mitsuhashi and Nagai, 1963). A better yield of LIII is obtained on limited hydrogenation.
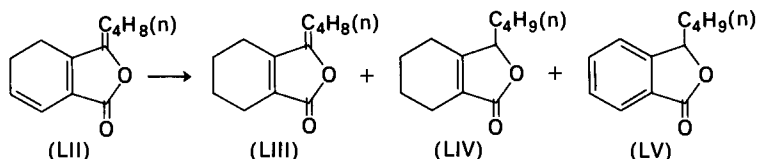
Disproportionation may be used deliberately as a source of hydrogen. A quantitative yield of 3,4-dicarboxyhydrocinnamic acid was obtained through an exchange reaction by refluxing the cinnamic acid in acetone and cyclohexene over palladium black for 68 hours (Clendinning and Rauscher, 1961).
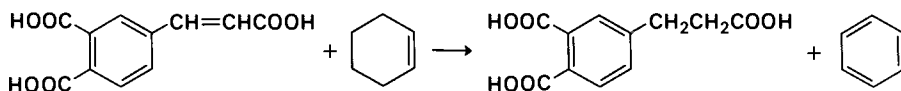
V. STEREOCHEMISTRY

The stereochemistry of hydrogenation of olefins* is such that hydrogen usually is added as if by *cis* addition from the catalyst to the side of the molecule that is adsorbed on it. However, as has been pointed out (Stork and Hill, 1957), it is not always easy to decide which side of the molecule will adsorb on the catalyst. The chance of correctly predicting the favored approach of the catalyst is increased when the substrate has a high degree of rigidity (Stork and Schulenberg, 1962). Correct prediction of the stereochemical outcome of olefin hydrogenation is further complicated by the possibility of prior isomerization over the hydrogenation catalyst. Hydrogenation of 1,2-dimethylcyclohexene over 5% palladium-on-alumina in acetic acid afforded 73% *trans*-1,2-dimethylcyclohexane, certainly an unexpected result. The percentage of *trans* isomer was changed by pressure and also by the presence of alkali (Siegel and Smith, 1960ab).

A. EXO-ADDITION

Addition of hydrogen to certain bridged polycyclic systems follows an exo-addition rule to give *endo* substituents. For example, hydrogenation of

* For a good review, see Siegel, 1966.

LVI over platinum oxide gave the *endo*-2,3-dicarboxylic acid (LVII). Attempt-
ed hydrogenations over palladium were unsuccessful (Cristol and LaLonde,
1959).

(LVI)   (LVII)
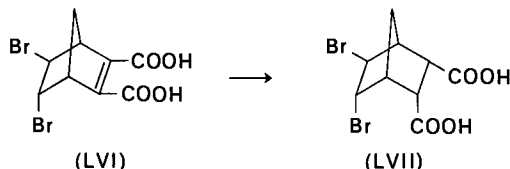
Other examples of the preference for exo-addition are hydrogenation of
bicyclo[2.2.1]hept-2-ene-2,3-dicarboxylic acid to give the *endo,cis*-2,3-
dicarboxylic acid, of bicyclo[2.2.1]hept-2-ene-2-carboxylic acid to give
endo-2-carboxylic acid (Alder *et al.*, 1936), and of 2,3-dimethylbicyclo[2.2.1]-
hept-2-ene to give the *endo,cis*-2,3-dimethyl compound (Alder and Roth,
1954). Reduction of each of a series of α-pinene derivatives over platinum
oxide in acetic acid proved highly stereoselective. Addition of hydrogen
was to the methylene-bridge side of the molecule (Eigenmann and Arnold,
1959).

B. Effect of Substituents

Various substituents may have a marked effect on the stereochemistry
of olefin saturation, inasmuch as these substituents may participate directly
in the reduction, as through 1,4- or 1,6-addition, or may alter the steric
requirements (Dauben and Rogan, 1957) or influence the preferred mode of
adsorption through "anchor" effects.

The stereochemistry of hydrogenation of various substituted octalins,
for instance, is influenced by both the position and nature of the substituents.
Hydrogenation of LVIII over 10% palladium-on-carbon in ethanol gave
products (LIX), whose stereochemistry varied with the angular substituent
(Burgstahler and Nordin, 1961).

(LVIII)   (LIX)

R = CH$_3$	*cis/trans*: 3/4
R = CHO	mostly *cis*
R = COOH	mostly *cis*
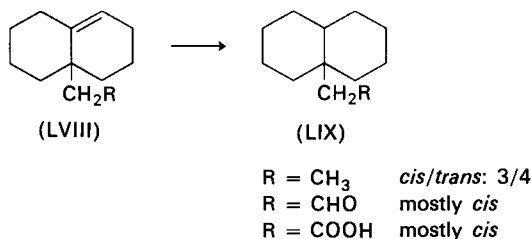
Hydrogenation of the unsaturated ketone (LX) over palladium-on-carbon
in ethanol or acetic acid gave the *trans*-decalone (LXI), but hydrogenation

of the acetoxy compound (LXII) gave the corresponding *cis*-decalone
(Halsall *et al.*, 1959).

(LX)   R = H
(LXII) R = CH₃CO—

(LXI)
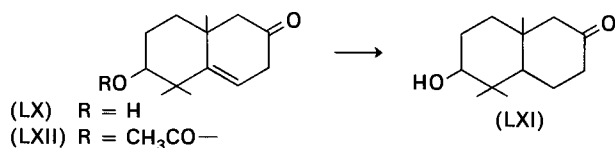
Similarly, hydrogenation of the dienone (LXIII) gave a *cis*-decalone
(LXIV), while hydrogenation of the corresponding dienol gave the *trans*-
compound (Haynes and Timmons, 1958).

(LXIII)   (LXIV)
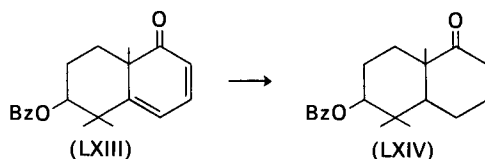
In some compounds the tendency to form a particular isomer is so strong
that only one product results regardless of the substituents. All efforts to
establish a *trans* ring junction by hydrogenation of LXV failed. The *cis* isomer
was always obtained despite the presence of bulky substituents introduced
in an effort to alter the course of reduction. The *cis* isomer was also obtained
when the double bond was in the five-membered ring (LXVI). Reduction of
LXVI over 2% palladium-on-calcium carbonate in ethanol followed by
hydrolysis after absorption of one equivalent of hydrogen, afforded the
cis-indane-1,5-dione. The selective reduction of one of two similarly substi-
tuted double bonds in LXVI is noteworthy (Boyce and Whitehurst, 1960).

(LXV)   (LXVI)
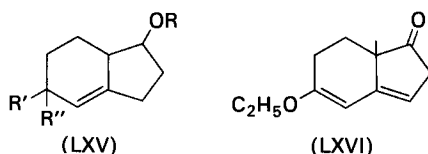
R = H, R′ = R″ = O
R′ = R=H R″ = —OH
R = H R′ = —OH R″ = C₆H₄OCH₃
R = —COC₆H₅ R′ = R″ = O

C. CATALYSTS

The reductions of LXVII over platinum oxide and over 10% palladium-
on-carbon in ethanol provide a striking example of the effect of catalyst on
stereospecificity. Reduction over platinum oxide afforded the saturated

cis isomer (LXVIII) in 95% yield, whereas over palladium-on-carbon a 95% yield of the *trans* isomer was obtained. The authors comment that, while it is tempting to suggest that over one of the catalysts prior isomerization of the double bond to an endocyclic position occurred, no evidence was obtained to support this hypothesis (Bergmann and Ikan, 1956). Perhaps one of the reductions involved carbethoxy group participation (Smith and Roth, 1965).
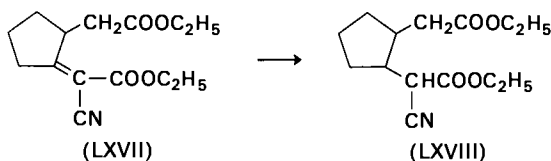
Different catalysts may give different stereochemical results through varying amounts of 1,2- and 1,4-addition. Hydrogenation of LXIX over platinum oxide was highly stereoselective, yielding only the *trans*-6β,9-dimethyldecahydronaphthalene derivative; both moles of hydrogen were added, stepwise by 1,2-addition, to the face opposite the angular methyl group. Over nickel, the reduction was nonselective but also afforded the *trans* isomer. Over palladium-on-calcium carbonate, only one equivalent of hydrogen was absorbed, apparently by 1,4-addition (LXX) (Nazarov *et al.*, 1956).
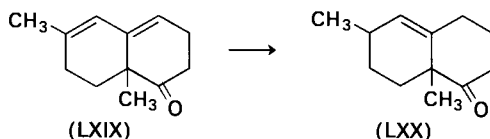
A complex relationship was found to exist between the products obtained on hydrogenation of $\Delta^{1,9}$-octalone-2 and the catalyst and solvent (Table II). Augustine (1963) has discussed the work in some detail, but suffice it to point

TABLE II

HYDROGENATION OF $\Delta^{1,9}$-OCTALONE-2

Solvent	Percent *cis*-β-Decalone		
	PtO$_2$	5% Rh/C	10% Pd/C[a]
Ethanol	62.7	69.6	44–65
Ethanol-HCl	77.5	86.9	80–89
Ethanol-NaOH	58.1	82.5	51–59

[a] Results were taken from a graph on the effect of the amount of catalyst on product. The range given is that achieved by changing only the amount of catalyst.

out that the products may be varied considerably by the solvent, catalyst, and amount of catalyst. Both the magnitude and direction of change in the percent of *cis* isomer formed in basic or acidic solvent depended on the catalyst and on the amount of catalyst. Inflections in curves obtained on plotting the percent of *cis* isomer vs. amount of catalyst occurred at just the amount of catalyst where diffusion control became prominent. Hydrogen availability at the catalyst surface was evidently a factor in determining the products.

The stereochemistry of reduction of LXXI depended on the amount of catalyst. The authors suggested that in the presence of a large amount of catalyst, where hydrogenation is relatively rapid, the catalyst surface becomes depleted in hydrogen. They interpreted their results in terms of a reversible half-hydrogenated state, where the chances of reversal increased as the catalyst surface became hydrogen-poor. The possibility that the results were due to isomerization of the *trans* (LXXII) to *cis* (LXXIII) isomer at high catalyst loading levels was ruled out (House *et al.*, 1962).
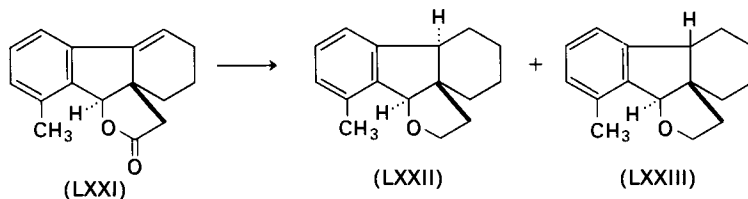
Weight ratio of substrate to catalyst	Percent (LXXII)	Percent (LXXIII)
5	19.5	55.5
10	40	28
40	52	31

The stereochemistry of reduction sometimes changes as the catalyst is altered through use, by additives, or by changes in its preparation. The percentages of the three products—coprostanol, cholestanol, and a saturated hydrocarbon—derived from hydrogenation of cholest-4-en-3β-ol over platinum oxide were determined in large measure by the method of preparation of the catalyst, by its pretreatment, and by the presence of various additives. [This reduction is discussed at length in Chapter 25 (Dart and Henbest, 1960).]

D. SOLVENT

Various explanations are advanced from time to time to account for the role of solvent in the stereochemistry of hydrogenation, or various rules

proposed to facilitate predictions, but inasmuch as the effect of solvent cannot always be divorced from the catalyst used or even the amount of catalyst, or from the substrate, the explanations, if true at all, must be limited and the rules must necessarily be used circumspectly. The examples that follow illustrate well the profound effect that the solvent may have, as well as some complexities.

Extensive work aimed at the selective and stereospecific reduction of stigmastadienone to 5β-stigmast-22-en-3-one was eminently successful, and illustrates the rather exacting conditions sometimes required:
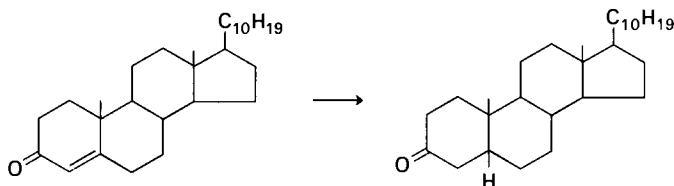
Conditions were found under which the above product was formed in 93% yield. Alkali was always necessary for good results but optimal concentrations were found to vary somewhat from one catalyst to another. For example, in isopropyl alcohol over 5% palladium-on-carbon the best results were obtained with a 4% catalyst loading based on steroid and a 21% potassium hydroxide level; over 5% palladium-on-zinc oxide a catalyst loading of 8% and a 5% potassium hydroxide level were best. Isopropanol proved better than methanol or ethanol because of good solubility characteristics. Reduction in Methyl Cellosolve was less stereospecific and in ethyl acetate (without alkali present) less selective, resulting in considerable saturation of the side chain. Selectivity could be increased by high catalyst loading levels, but stereospecificity decreased. Substitution of sodium hydroxide in place of potassium hydroxide resulted in lowered stereospecificity, as did the use of lower concentrations of substrate (Slomp et al., 1955).

In contrast to the above and other work (Chemerda et al., 1951; Yashin et al., 1951; Gabbard and Segaloff, 1962; Mancera et al., 1953), the use of alkali in hydrogenation of cortisone acetate was found to be detrimental. Good yields of the allopregnane product were obtained by hydrogenation of cortisone acetate in neutral solution, using tetrahydrofuran or ethyl acetate as the solvent and 5% palladium-on-carbon as catalyst. No evidence was obtained for the presence of the cis A/B ring isomer (Oliveto et al., 1952). The effect of alkali on the stereochemistry of reduction of olefins and of unsaturated ketones in the steroid ring system has been discussed at some length (Wilds et al., 1950).

A number of 3-substituted Δ^4-steroids were reduced under acidic conditions to give products of both the A/B-trans and A/B-cis series. Reductions were carried out over platinum oxide in ethyl acetate and in ethyl acetate

containing acetic, sulfuric, or perchloric acid. The presence of small amounts
of acids increased the rate but did not alter the stereochemical pattern.
Better yields of saturated products were obtained with acetic acid than with
sulfuric or perchloric acid; considerably less hydrogenolysis occurred with
acetic acid (Shoppee et al., 1957). The influence of solvent on the stereo-
chemistry of steroid reduction has been discussed at some length by
McQuillin et al., (1963).

The pH had a marked effect on the stereochemistry of reductions of hydro-
phenanthrones. Reduction of **LXXIV** over palladium-on-carbon in methanol
containing potassium hydroxide gave exclusively the *cis* ketone, whereas
reduction in ethyl acetate containing sulfuric acid gave equal amounts of the
cis and *trans* isomers (**LXXV**) (Wenkert and Jackson, 1959).

(LXXIV)   (LXXV)

While reduction in alkaline solution as above sometimes favors formation
of *cis-* rather than *trans*-decalones, reduction over palladium-on-carbon
of **LXXVI** gave predominantly the *cis-* and of **LXXVII** predominantly the
trans-decalone regardless of whether the solution was neutral or alkaline
(McQuillin and Ord, 1959). Reduction of **LXXVIII**, in contradiction to
earlier reports, always gave preponderantly the *cis* ketone regardless of the
solvent, catalyst, or presence of acid or base (van Tamelen and Proost,
1954). Reductions of α,β-unsaturated ketones in the hexahydroindane series
always gave predominantly a *cis* ring juncture regardless of the position of
the unsaturation, the type of angular substituent, or the pH of the reduction
medium (Dauben et al., 1961).

(LXXVI)   (LXXVII)   (LXXVIII)

Hydrogenation of 2-methyl-3-phenylindone over platinum oxide in
ethyl acetate or benzene gave the *cis* isomer; in ethyl acetate–ethanol contain-
ing sodium hydroxide the *trans* isomer was formed. The more stable *trans*

isomer would be expected to be formed in alkaline solution, since alkaline conditions allow epimerization at the α-carbon atom (Zimmerman, 1956).

VI. OLEFIN SATURATION IN POLYFUNCTIONAL MOLECULES

Many molecules contain olefins together with other reducible functions. In this section, the problem of selectively reducing the olefin in such molecules is considered.

A. α,β-UNSATURATED ALDEHYDES

Reduction of aliphatic α,β-unsaturated aldehydes to saturated aldehydes is readily achieved by most platinum metal catalysts under mild conditions, in various solvents, in batch or continuous processing, and in liquid or vapor phase. Reduction of aromatic α,β-unsaturated aldehydes, such as cinnamaldehyde, to the saturated aldehyde is more difficult because the carbonyl is frequently partially reduced as well. Although the aliphatic saturated aldehyde can be obtained in high yield by reduction over palladium, platinum, rhodium, and ruthenium on a variety of supports, it seems that, except in some unusual circumstances, palladium is the metal of choice. Palladium makes an extremely active catalyst for carbon–carbon double bond saturation, but is the least active of these metals for aliphatic carbonyl reduction. A highly selective reduction is obtained automatically when using palladium, for the reduction virtually stops after absorption of one equivalent of hydrogen, except under vigorous conditions.

In batch processing, the reduction proceeds rapidly even at atmospheric pressure and room temperature. The rate increases as the temperature and pressure are raised. For most unsaturated aldehydes, convenient rates are obtained within the ranges 20–80°C, 0–1500 psig, and 0.1–1.5% catalyst. A satisfactory catalyst for this type of reduction is 5% palladium-on-carbon or -on-alumina. For instance, crotonaldehyde was reduced to butyraldehyde at atmospheric pressure and room temperature by 200 mg 5% palladium-on-carbon at a rate of 100 ml hydrogen absorbed per minute (Rylander *et al.*, 1963).

The preparation of a platinum–palladium-on-magnesia catalyst for selective hydrogenation of unsaturated aldehydes has been described by Lacey (1960). Wet crotonaldehyde is converted in 95% yield to butyraldehyde at 140°C and 15 psig in continuous passage over a 0.2% palladium-on-magnesia catalyst (Lacey, 1959a,b). Rhodium- or ruthenium-on-carbon has been claimed to be superior to platinum-on-carbon for conversion of acrolein to propionaldehyde (Howsmon, 1962). Hydrogenation of the

sesquiterpene aldehyde, sinensal (LXXIX), over platinum oxide in ethanol at 1 atm ceased after saturation of the conjugated olefins, selectively affording LXXX. When the reduction was carried out over 5% platinum-on-carbon the completely saturated alcohol (LXXXI) was formed (Stevens et al., 1965).

(LXXXI)   (LXXIX)   (LXXX)
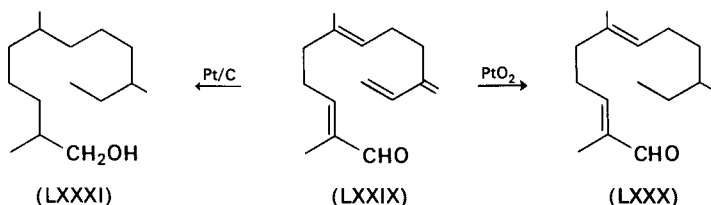
Reduction of cinnamaldehyde was shown to be influenced by the catalyst carrier, and by the amount of catalyst (Csuros, 1951). Palladium-on-barium sulfate and palladium-on-strontium carbonate gave more products derived by hydrogenolysis than did palladium-on-calcium carbonate. Over platinum oxide, hydrocinnamaldehyde was obtained in high yield accompanied by products derived from decarbonylation (Fukuda, 1962). (The reduction of this compound is discussed at greater length in Chapter 14 on aldehydes.)

1. Nonconjugated Unsaturated Aldehydes

Ordinarily the olefinic function in compounds of this type may be easily reduced preferentially over catalysts like palladium, which have low activity for reduction of the aldehyde group. Citronellal was reduced preferentially at the carbon–carbon double bond over platinum oxide or palladium-on-barium sulfate, but with a nickel-on-kieselguhr catalyst the carbonyl was reduced first (Ishikawa and Hyo, 1948).

Occasionally special techniques are required to obtain satisfactory results. Cyclohexanecarboxaldehyde has been obtained in 81% yield and 99% purity by selective hydrogenation of 3-cyclohexene-1-carboxaldehyde without solvent over 5% palladium-on-carbon at 75–80°C and 200 psig. A hydrogenation vessel with good agitation is necessary, if satisfactory results are to be obtained. Hydrogenation in a rocker bomb was unsuccessful; reduction was too slow to be practical with the above conditions and selectivity decreased if the temperature were raised. Successful reductions were carried out in a stirred type of autoclave (Hennis and Trapp, 1961). This procedure obviated the necessity of slurrying the substrate with Raney nickel prior to reduction over palladium (Heilbron et al., 1949).

B. α,β-UNSATURATED KETONES

The course of reduction of α,β-unsaturated ketones, RCOCH=CHR', depends in large measure on the nature of R and R'. When R and R' are both

aliphatic the olefinic function usually may be selectively reduced with ease. Palladium is a useful catalyst since it reduces the carbon–carbon double bond rapidly and the carbonyl slowly. Platinum, rhodium, and ruthenium are apt to carry the reduction further to the saturated alcohol if the reaction is not interrupted (Breitner *et al.*, 1959). Acetylcycloheptene afforded acetyl-cycloheptane in 97% yield when reduced over 5% palladium-on-carbon in methanol (Taub and Szmuszkovicz, 1952). Tropones were reduced over either platinum oxide or 10% palladium-on-carbon to cycloheptanones (Doering and Hiskey, 1952). Tetrahydro-1,4-pyrone was obtained in 75% yield, after distillation, by reduction of 1,4-pyrone in methanol over palladium-on-strontium carbonate at 150 psig (Sorkin *et al.*, 1948). Chemical methods of reduction of γ-pyrones generally result in ring fission (Rodd, 1959).

It is said that improved yields of saturated ketones are obtained from α,β-unsaturated ketones if the reduction is carried out in the presence of a secondary amine with platinum or palladium catalysts (Drishaus, 1952). The following example illustrates an application of this technique. Stereo-specific hydrogenation of 7-keto-Δ⁵-androstene-3β,17β-diol diacetate to 7-ketoandrostane-3β,17β-diol diacetate over 10% palladium-on-carbon in methanol initially offered some difficulty. The yields were only about 50%, presumably because of some reduction of the 7-keto function. The yields were raised to 90% when a small amount of pyridine was added to the reduction (Ringold, 1960).
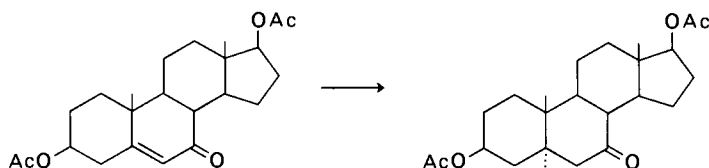
When R in RCOCH=CHR' is aromatic, a selective reduction of the olefin can still be achieved, but the reduction should as a rule be stopped after absorption of one mole of hydrogen, regardless of the catalyst, since aromatic ketones are often reduced with considerable ease. Palladium would seem to be the catalyst of choice, as suggested by the following examples. Palladium-on-carbon proved much superior to platinum oxide for reduction of 2-benzylidene-1-indanone in methanol to the saturated ketone (LXXXII). Over palladium this product was obtained in 80% yield when the reduction was stopped after absorption of one equivalent of hydrogen. Palladium-on-barium sulfate in ethanol also gave good results (Campbell *et al.*, 1963). Cromwell and Ayer (1960) also preferred palladium to platinum oxide in reduction of 2-benzylidene-1-indanones. The course and stereospecificity of

reduction of a number of compounds of this type over a variety of catalysts have been the subject of an extensive investigation (Hückel et al., 1958).
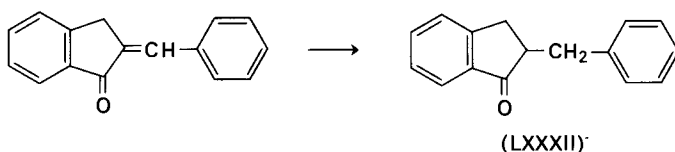
(LXXXII)·

Other reactions besides reduction of the carbonyl may occur in certain systems. Reduction of *trans*-1,4-diphenyl-2-butene-1,4-dione (LXXXIII) gave several products in varying amounts, which depended to a large extent on the catalyst. In platinum-catalyzed reductions, LXXXIV, LXXXV, and LXXXVI were formed as well as LXXXVII. Over 10% palladium-on-carbon in isopropanol-hydrochloric acid solvent at room temperature and atmospheric pressure, LXXXVII was obtained in 67% yield (Kreutzberger and Kalter, 1960). Dimerization may be prevented by addition of ferric chloride or by carrying out the reduction at reflux (Weygand and Meusel, 1943). The reduction of dibenzoylethylene was examined in detail by Lutz and Palmer (1935), who noted that under conditions where the *trans* isomer is reduced chiefly to the dimolecular product, the *cis* isomer gives mainly dibenzoylethane (LXXXVII). The products obtained in reduction of LXXXIII over palladium-on-carbon catalysts depend on the method of catalyst preparation and on the presence of acid or alkali (Imanura, 1963). Dimerization of α,β-unsaturated ketones has been accounted for in a general mechanism of reduction for this class of compounds (Weidlich and Meyer-Delius, 1941).
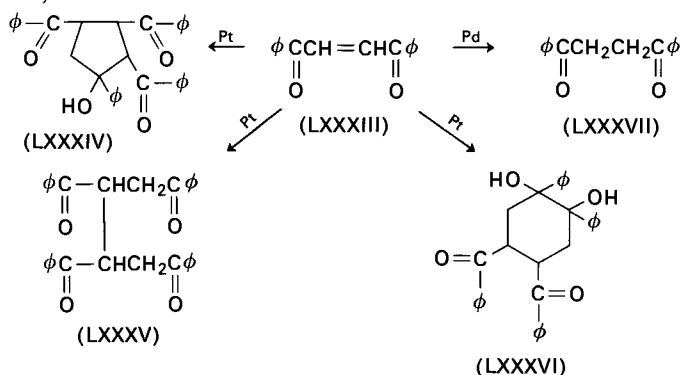
When R′ in RCOCH=CHR′ is aromatic, the system may be viewed as a vinylog of an aromatic ketone, and reduction of the ketone is apt to proceed prior to or concomitant with reduction of the double bond. Palladium has proved more selective than platinum in reductions of this type. For instance, catalytic reduction of 2-benzylidenecyclopentanone over palladium-on-carbon in methanol proceeded with absorption of only one mole of hydrogen

to give 2-benzylcyclopentanone in high yield. But in a reduction over platinum oxide, 80% of two moles were absorbed and a mixture of 2-benzyl-cyclopentanone and 2-benzylcyclopentanol was formed. The authors suggest that the mixture is formed because the reduction can proceed through multiple routes (Phillips and Mentha, 1956).
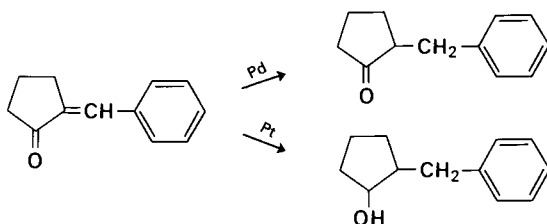
Some unsaturated ketones, while not containing an aromatic system per se, yield an aromatic system through disproportionation during the reduction. For instance, reduction of the dienone (LXXXVIII) over 5% palladium-on-carbon in ether gave a mixture consisting of about 20% indane, 20% cis-hexahydro-1-indanone, and 45% 4,5,6,7-tetrahydro-1-indanone (House and Rasmusson, 1963).

(LXXXVIII)
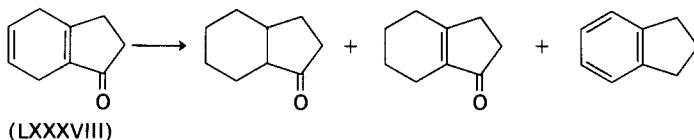
1. Participation of the Carbonyl

There is considerable evidence to indicate that reduction of the olefinic function in conjugated unsaturated ketones may involve participation of the ketone. The hydrogenation of XXVI provides one such example (Miropol-'skaya et al., 1962). The same unsaturated system is found in a steroid (LXXXIX), which on reduction over palladium or platinum catalysts in the presence of a proton acceptor, such as triethylamine, gave entirely the

(LXXXIX)
X=Cl, Br

(XC)
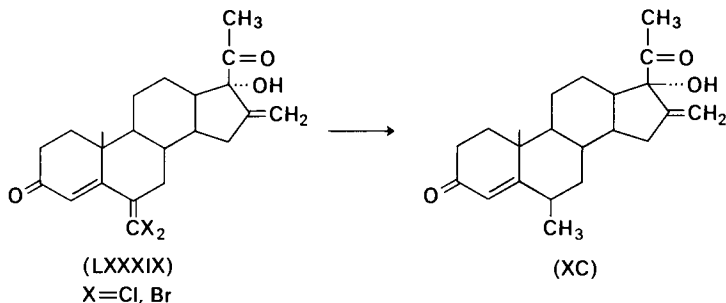
corresponding 6α-methyl compound (XC) without reduction of the 16-methylene group. The inventor pointed out that this surprising selective reduction is without analogy in the field of steroids (Bork, 1964).

Participation of the ketone function was believed to account for the facile hydrogenation over palladium of the usually resistant tetrasubstituted double bond in Δ^8-unsaturated 7-keto steroids, leading directly to B/C-*trans* (8β, 9α) juncture (Djerassi *et al.*, 1952). The corresponding Δ^8-11-ketone required at least 10 times as long for complete reduction (Djerassi *et al.*, 1953). Involvement of the carbonyl as an enol is also believed to account for some of the observed effects of solvent on selectivity in dienone systems (Shepherd *et al.*, 1955; Woodward *et al.*, 1952).

C. UNSATURATED ALCOHOLS AND ETHERS

Reduction of unsaturated alcohols and ethers, with the exception of allylic and vinylic systems, usually presents no problem. The alcohol or ether function is inert in most instances and the molecule can be treated as if it were a hydrocarbon. Certain structures may allow involvement of an alcohol removed from the site of unsaturation. For instance, catalytic hydrogenation of 5-cyclodecen-1-ol over platinum oxide in methanol resulted in absorption of 0.97 molar equivalent of hydrogen to give the saturated alcohol. However, when 10% palladium-on-carbon in alcohol was used as a catalyst, reduction was incomplete due to formation of cyclo-decanone through an exchange reaction. The exceptional ease of this type of reaction in this case was explained by the spatial proximity of the alcohol and olefin groups, favoring an intramolecular hydrogen transfer (Cope *et al.*, 1955). A similar transfer may also have occurred in the presence of platinum, but might pass unobserved as platinum would reduce the ketone so formed to the alcohol.
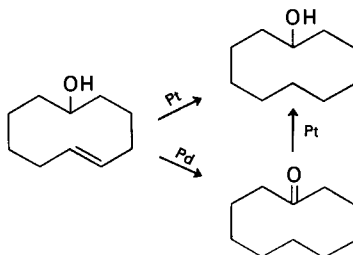
Allylic and Vinylic Systems

Reduction of the unsaturation in allylic and vinylic oxygen systems may be complicated by concomitant hydrogenolysis of the oxygen function in varying degrees, by isomerization to carbonyl compounds, by double-bond

migration, by allylic rearrangements, and by dimerization. (These reactions are discussed at some length in Chapter 25). In general, hydrogenolysis is increased by acids and decreased by bases, but this is not always the case. Bases promoted hydrogenolysis of phenyl cinnamyl ether, a compound that in the absence of additives was reduced without hydrogenolysis over palladium-on-carbon. The increased hydrogenolysis in the presence of bases was attributed to easier desorption of acids formed by hydrogenolysis (Oshima *et al.*, 1963).

An interesting technique for achieving saturation of an allylic system especially prone to hydrogenolysis has been described by Nickon and Bagli (1961). A mixture of 0.52 gm XCI and 0.24 gm 10% palladium-on-carbon in 40 ml dry ether was hydrogenated at $-27°C$ in an apparatus equipped with a mercury-filled manometer and burette. Two recrystallizations of the product afforded XCII in 55% yield. When water-filled leveling burettes were used, hydrogenation was incomplete presumably because of water condensation in the cold reaction flask.
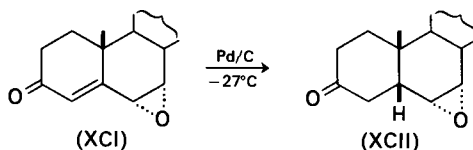
Several examples of the use of rhodium in reduction of allylic oxygen compounds with minimum hydrogenolysis have been cited (page 84). Ruthenium has also proved useful in this type of reduction. The unsaturated diacetate (XCIII) undergoes hydrogenolysis readily and over platinum oxide absorbed 172% of one molar equivalent, and over ruthenium dioxide 144%. The reduction with ruthenium was carried out with 100 mg prereduced ruthenium dioxide, 5.5 gm XCIII, and 30 ml 95% ethanol (Cope *et al.*, 1957).
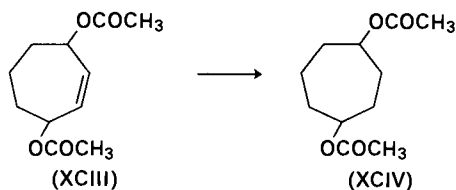
D. UNSATURATED HYDROXYLAMINES

Unsaturated hydroxylamines may be reduced to the corresponding saturated compounds in good yield if hydrogen absorption is limited to one equivalent. Further absorption results in hydrogenolysis of the nitrogen–oxygen bond. *N*-Methyl-*N*-*n*-heptylhydroxylamine (XCV) was obtained in

84% yield by hydrogenation of 1 gm XCVI in 15 ml methanol over 0.3 gm prereduced 1.5% palladium-on-calcium carbonate. Hydrogenation of 1 gm XCVI in 13 ml acetic acid afforded methyl-*n*-heptylamine in 97% yield (Cope and LeBel, 1960).

$$CH_3CH_2(CH_2)_5NHCH_3 \xleftarrow{2H_2}{Pt} CH_2{=}CH(CH_2)_5\overset{CH_3}{\underset{|}{N}}OH \xrightarrow{H_2}{Pd} CH_3CH_2(CH_2)_5\overset{CH_3}{\underset{|}{N}}OH$$
$$(XCVI) \qquad\qquad\qquad\qquad (XCV)$$
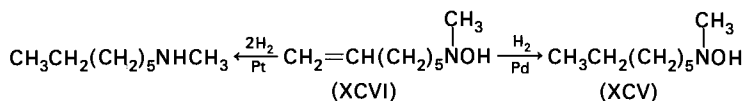
E. UNSATURATED NITRO COMPOUNDS

Unsaturated nitro compounds usually may be reduced selectively with ease to the corresponding saturated nitro compound, if the nitro group is not aromatic. Reductions of this type are usually carried out over palladium or platinum catalysts (deMauny, 1940; Roberts *et al.*, 1954; Freeman, 1960), and stopped after one equivalent of hydrogen has been absorbed if the absorption does not stop spontaneously (Sowden and Fischer, 1947). Even tetrasubstituted double bonds may be selectively reduced. Hydrogenation of 38 gm XCVII in 175 ml ethanol over 3 gm 5% palladium chloride-on-carbon afforded, after absorption of one equivalent of hydrogen, XCVIII in 89% yield. In this substrate, hydrogenation may have been facilitated by 1,4-addition (Feuer and Harmetz, 1961). (The reduction of unsaturated nitro compounds is discussed at greater length in Chapter 11).

(XCVII)   (XCVIII)
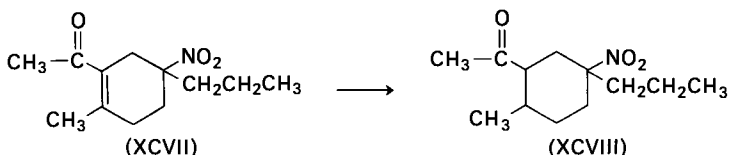
F. UNSATURATED NITRILES

The carbon–carbon double bond is in general reduced much more readily than the nitrile function, and a selective reduction presents little difficulty. Even under fairly vigorous conditions the selectivity is maintained, as indicated in the following reductions of dicyanobutene to adiponitrile.

$$NCCH_2CH{=}CHCH_2CN \longrightarrow NC(CH_2)_4CN$$
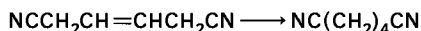
Dicyanobutene was reduced in a slurry over palladium-on-carbon at 30–40°C and 400 psig to adiponitrile in quantitative conversion and 90% yield. Alcohols, water, ether, or acetonitrile were used as solvents (Romilly,

1950). The hydrogenation may be done also in the gas phase over palladium-on-carbon catalyst at 250–300°C and 15–75 psig with 10–100 mole excess of hydrogen (Howk and Farlow, 1950; Calkins and Welton, 1956).

Palladium is a popular catalyst for this type of selective reduction. 3-Methylenecyclobutanecarbonitrile was selectively reduced over palladium oxide in ethanol to the 3-methyl derivative. The reduction was stopped after one equivalent of hydrogen had been absorbed (Cripps *et al.*, 1959). Similarly, unsaturated nitrile esters were selectively reduced over 10% palladium-on-carbon in ethanol to saturated nitrile esters (Brockman and Fabio, 1957). 2-Cyano-2-*n*-propyl-6-methoxytetralone-1 (0.26 gm) was prepared by selective reduction of 0.30 gm of the corresponding 2-allyl compound over 16% palladium-on-carbon in ethanol (Nomine *et al.*, 1963). Cycloalkylacetonitriles were prepared in high yield by selective hydrogenation of the corresponding 1-cycloalkenylacetonitriles over 5% palladium-on-carbon in ethanol (Whitehead *et al.*, 1961).

Although increasing substitution hinders reduction of a carbon–carbon double bond, a tetrasubstituted olefin was selectively reduced in the presence of a nitrile function over platinum oxide in ethanol. The reduction was carried out until 3–5% more than the theoretical had been absorbed. The product, ethyl 2-carbethoxycyclopentanylcyanoacetate, was isolated in 86% yield after distillation (Anderson *et al.*, 1963). The reduction may have been facilitated by participation of the carbonyl function.
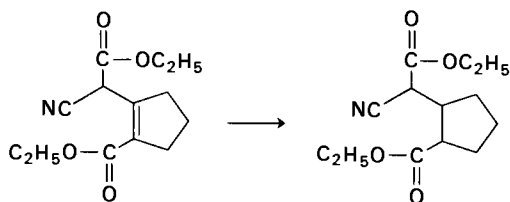
G. SULFUR-CONTAINING OLEFINS

Reduction of compounds containing oxidized sulfur can usually be done without difficulty. Oxidized sulfur has few toxic qualities toward platinum metals. Sulfuric acid, for instance, makes an excellent solvent for many platinum metal-catalyzed reductions. Divalent sulfur, on the other hand, severely inhibits catalyst activity. Nonetheless, sulfur-containing olefins can be successfully reduced with high catalyst loadings or vigorous conditions. Palladium is probably less likely to be poisoned than platinum (Markgraf *et al.*, 1964).

Ketene di-*n*-butyl mercaptal was reduced to acetaldehyde di-*n*-butyl mercaptal over palladium-on-alumina in isopropyl alcohol at 102–110°C

and 800–1000 psig. A 7% catalyst loading based on substrate was used. Approximately 98% of the theoretical hydrogen was absorbed, in an unspecified time, and the product was obtained in 73% yield (Schneider *et al.*, 1961).

$$CH_2{=}C(SC_4H_9)_2 \longrightarrow CH_3CH(SC_4H_9)_2$$
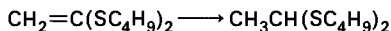
A 68% yield of 1-chloro-1-phenylmercaptobutene-1 was obtained by reduction of the corresponding diene over 5% palladium-on-barium sulfate in absolute ethanol. In this reduction, 28 gm catalyst was used with 7.0 gm substrate.
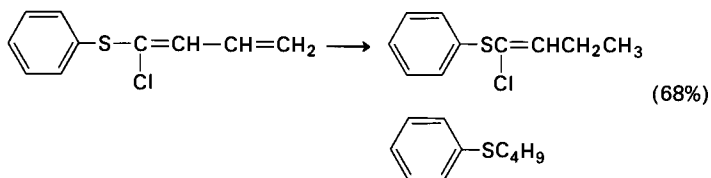
In another similar reduction, 1-*t*-butylmercapto-1-chlorobutadiene (10 gm) was reduced in absolute ethanol over 26 gm 5% palladium-on-barium sulfate to *cis,trans*-1-*t*-butylmercapto-1-chlorobutene-1 (Parham and Groen, 1964). Hydrogenation of sulfur containing compounds is discussed further in Chapter 1.

REFERENCES

Adams, R., and Gianturco, M., *J. Am. Chem. Soc.* **79**, 166 (1957).

Addor, R. W., Personal communication, 1964.

Alder, K., and Roth, W., *Chem. Ber.* **87**, 161 (1954).

Alder, K., Stein, G., Schneider, S., Liebmann, M., Rolland, E., and Schultze, G., *Ann. Chem. Liebigs* **525**, 183 (1936).

Anderson, A. G., Jr., Harrison, W. F., and Anderson, R. G., *J. Am. Chem. Soc.* **85**, 3448 (1963).

Anderson, M., and Johnson, A. W., *Proc. Chem. Soc.* p. 263 (1964).

Augustine, R. L., *J. Org. Chem.* **28**, 152 (1963).

Bal'yan, Kh. V., Petrov, A. A., Borovikova, N. A., Kormer, V. A., and Yakovleva, T. V., *Zh. Obshch. Khim.* **30**, 3247 (1960).

Barton, D. H. R., and Seoane, E., *J. Chem. Soc.* p. 4150 (1956).

Bellinzona, G., and Bettinetti, G. F., *Gazz. Chim. Ital.* **90**, 426 (1960).

Bergmann, E. D., and Ikan, R., *J. Am. Chem. Soc.* **78**, 1482 (1956).

Berkowitz, L. M., and Rylander, P. N., *J. Org. Chem.* **24**, 708 (1959).

Bond, G. C., and Rank, J. S., *Proc. 3rd Intern. Congr. Catalysis, Amsterdam, 1964* Vol. II, p. 1225. North-Holland Publ., Amsterdam, 1965.

Bond, G. C., and Wells, P. B., *Advan. Catalysis* **15**, 92 (1964).

Bond, G. C., Webb, G., Wells, P. B., and Winterbottom, J. M., *J. Chem. Soc.* p. 3218 (1965).

Bonner, W. A., Stehr, C. E., and doAmaral, J. R., *J. Am. Chem. Soc.* **80**, 4732 (1958).

Bonner, W. A., Burke, N. I., Fleck, W. E., Hill, R. K., Joule, J. A., Sjöberg, B., and Zalkow, J. H., *Tetrahedron* **20**, 1419 (1964).

Bork, K.-H., U.S. Patent 3,157,679, Nov. 17, 1964.

Boyce, C. B. C., and Whitehurst, J. S., *J. Chem. Soc.* p. 4547 (1960).

Bream, J. B., Eaton, D. C., and Henbest, H. B., *J. Chem. Soc.* p. 1974 (1957).

Breitner, E., Roginski, E., and Rylander, P. N., *J. Org. Chem.* **24**, 1855 (1959).

Brockman, J. A., Jr., and Fabio, P. F., *J. Am. Chem. Soc.* **79**, 5027 (1957).

Burgstahler, A. W., and Nordin, I. C., *J. Am. Chem. Soc.* **83**, 198 (1961).

Calkins, W. H., and Welton, D. E., U.S. Patent 2,749,359, June 5, 1956.

Campbell, N., Davison, P. S., and Heller, H. G., *J. Chem. Soc.,* p. 993 (1963).

Chanley, J. D., and Mezzetti, T., *J. Org. Chem.* **29**, 228 (1964).

Chapman, O. L., Smith, H. G., and Barks, P. A., *J. Am. Chem. Soc.* **85**, 3171 (1963).

Chemerda, J. M., Chamberlain, E. M., Wilson, E. H., and Tishler, M., *J. Am. Chem. Soc.* **73**, 4052 (1951).

Clendinning, R. A., and Rauscher, W. H., *J. Org. Chem.* **26**, 2963 (1961).

Cookson, R. C., Hamon, D. P. G., and Parker, R. E., *J. Chem. Soc.* p. 5014 (1962).

Cope, A. C., and Campbell, H. C., *J. Am. Chem. Soc.* **74**, 179 (1952).

Cope, A. C., and LeBel, N. A., *J. Am. Chem. Soc.* **82**, 4656 (1960).

Cope, A. C., Haven, A. C., Jr., Ramp, F. L., and Trumbull, E. R., *J. Am. Chem. Soc.* **74**, 4867 (1952).

Cope, A. C., Cotter, R. J., and Roller, G. G., *J. Am. Chem. Soc.* **77**, 3594 (1955).

Cope, A. C., Liss, T. A., and Wood, G. W., *J. Am. Chem. Soc.* **79**, 6287 (1957).

Corson, B. B., *Catalysis* **3**, 79 (1955).

Cram, D. J., *J. Am. Chem. Soc.* **74**, 5518 (1952).

Cripps, H. N., Williams, J. K., and Sharkey, W. H., *J. Am. Chem. Soc.* **81**, 2723 (1959).

Cristol, S. J., and LaLonde, R. T., *J. Am. Chem. Soc.* **81**, 1655 (1959).

Cristol, S. J., Russell, T. W., and Davies, D. I., *J. Org. Chem.* **30**, 207 (1965).

Cromwell, N. H., and Ayer, R. P., *J. Am. Chem. Soc.* **82**, 133 (1960).

Csuros, Z., *Research (London)* **4**, 52 (1951).

Dart, M. C., and Henbest, H. B., *J. Chem. Soc.* p. 3563 (1960).

Dauben, W. G., and Rogan, J. B., *J. Am. Chem. Soc.* **79**, 5002 (1957).

Dauben, W. G., McFarland, J. W., and Rogan, J. B., *J. Org. Chem.* **26**, 297 (1961).

Dawson, M. C., Halsall, T. G., Jones, E. R. H., Meakins, G. D., and Phillips, P. C., *Chem. Ind. (London)* p. 918 (1955).

deMauny, H. C., *Bull. Soc. Chim. France* **7**, 133 (1940).

DePuy, C. H., and Story, P. R., *J. Am. Chem. Soc.* **82**, 627 (1960).

deVivar, A. R., Bratoeff, E. A., and Ríos, T., *J. Org. Chem.* **31**, 673 (1966).

Djerassi, C., Bates, E., Velasco, M., and Rosenkranz, G., *J. Am. Chem. Soc.* **74**, 1712 (1952).

Djerassi, C., Frick, W., Rosenkranz, G., and Sondheimer, F., *J. Am. Chem. Soc.* **75**, 3496 (1953).

Dobson, N. A., Eglinton, G., Krishnamurti, M., Raphael, R. A., and Wells, R. G., *Tetrahedron* **16**, 16 (1961).

Doering, W. von E. and Hiskey, C. F., *J. Am. Chem. Soc.* **74**, 5688 (1952).

Drishaus, I., German Patent 828,244, Jan. 17, 1952.

Eglinton, G., Jones, E. R. H., Mansfield, G. H., and Whiting, M. C., *J. Chem. Soc.* p. 3197 (1954).

Eigenmann, G. W., and Arnold, R. T., *J. Am. Chem. Soc.* **81**, 3440 (1959).

Eisenbraun, E. J., George, T., Riniker, B., and Djerassi, C., *J. Am. Chem. Soc.* **82**, 3648 (1960).

Farmer, E. H., and Galley, R. A. E., *J. Chem. Soc.* p. 687 (1933). Farmer, E. H., and Galley, R. A. E., *Nature* **131**, 60 (1933).

Feuer, H., and Harmetz, R., *J. Org. Chem.* **26**, 1061 (1961).

Freeman, J. P., *J. Am. Chem. Soc.* **82**, 3869 (1960).

Freidlin, L. Kh., and Polkovnikov, B. D., *Dokl. Akad. Nauk SSSR* **112**, 83 (1957).

Freidlin, L. Kh., Polkovnikov, B. D., and Egorov, Yu. P., *Izv. Akad. Nauk SSSR Otd. Khim. Nauk* p. 910 (1959).

Freidlin, L. Kh., Litvin, E. F., and Krylova, L. M., *Neftekhimiya* **5**, 468 (1965).

Fujita, K., and Matsuura, T., *J. Sci. Hiroshima Univ.* **A18**, 455 (1955).

Fukuda, T., *Nippon Kagaku Zasshi* **83** (10), 1122 (1962).

Gabbard, R. B., and Segaloff, A., *J. Org. Chem.* **27**, 655 (1962).

Gardner, P. D., and Narayana, M., *J. Org. Chem.* **26**, 3518 (1961).

Garrett, E. R., Donia, R. A., Johnson, B. A., and Scholten, L., *J. Am. Chem. Soc.* **78**, 3340 (1956).

Gregory, G. I., Hunt, J. S., May, P. J., Nice, F. A., and Phillipps, G. H., *J. Chem. Soc.* (C) p. 2201 (1966).

Halsall, T. G., Rodewald, W. J., and Willis, D., *J. Chem. Soc.* p. 2798 (1959).

Ham, G. E., and Coker, W. P., *J. Org. Chem.* **29**, 194 (1964).

Hasek, R. H., Gott, P. G., and Martin, J. C., *J. Org. Chem.* **29**, 2513 (1964).

Haynes, N. B., and Timmons, C. J., *Proc. Chem. Soc.* p. 345 (1958).

Heilbron, I. M., Jones, E. R. H., Richardson, R. W., and Sondheimer, F., *J. Chem. Soc.* p. 737 (1949).

Hennis, H. E., and Trapp, W. B., *J. Org. Chem.* **26**, 4678 (1961).

Hershberg, E. B., Oliveto, E., Rubin, M., Staeudle, H., and Kuhlen, L., *J. Am. Chem. Soc.* **73**, 1144 (1951).

Herz, W., Ueda, K., and Inayama, S., *Tetrahedron* **19**, 483 (1963).

Herz, W., Kishida, Y., and Lakshmikantham, M. V., *Tetrahedron* **20**, 979 (1964).

House, H. O., and Rasmusson, G. H., *J. Org. Chem.* **28**, 27 (1963).

House, H. O., Carlson, R. G., Müller, H., Noltes, A. W., and Slater, C. D., *J. Am. Chem. Soc.* **84**, 2614 (1962).

Howk, B. W., and Farlow, M. W., U.S. Patent 2,532,311, Dec. 5, 1950.

Howsmon, W. B., Jr., U.S. Patent 3,056,840, Oct. 2, 1962.

Hückel, W., Maier, M., Jordan, E., and Seeger, W., *Ann. Chem. Liebigs* **616**, 46 (1958).

Huffman, J. W., *J. Org. Chem.* **24**, 447 (1959).

Huntsman, W. D., Madison, N. L., and Schlesinger, S. I., *J. Catalysis* **2**, 498 (1963).

Imamura, Y., *Nippon Kagaku Zasshi* **84** (5) 416 (1963).

Ishikawa, S., and Hyo, B., *Kagaku Kenkyusho Hokoko* **24** (4), 113 (1948).

Jardine, I., and McQuillin, F. J., *J. Chem. Soc.* p. 458 (1966).

Johnston, A. E., MacMillan, D., Dutton, H. J., and Cowan, J. C., *J. Am. Oil Chemists' Soc.* **39**, 273 (1962).

Kaye, I. A., and Matthews, R. S., *J. Org. Chem.* **29**, 1341 (1964).

Kazanskii, B. A., Gostunskaya, I. V., Popova, N. I., and Dobroserdova, N. B., *Vestn. Mosk. Univ. Ser. Mat. Mekhan. Astron. Fiz. i Khim.* **13**, 207 (1958).

Keith, C. D., and Rylander, P. N., U.S. Patent 3,221,078, Nov. 30, 1965.

Kern, J. W., Shriner, R. L., and Adams, R., *J. Am. Chem. Soc.* **47**, 1147 (1925).

Kidwai, A. R., and Devasia, G. M., *J. Org. Chem.* **27**, 4527 (1962).

Kindler, K., Oelschläger, H., and Henrich, P., *Chem. Ber.* **86**, 167 (1953).

Kreutzberger, A., and Kalter, P. A., *J. Org. Chem.* **25**, 554 (1960).

Kuhn, R., and Fischer, H., *Chem. Ber.* **93**, 2285 (1960).

Lacey, R. N., British Patent 814,003, May 27, 1959a.

Lacey, R. N., British Patent 816,151, July 8, 1959b.

Lacey, R. N., U.S. Patent 2,930,766, Mar. 29, 1960.

Larrabee, C. E., and Craig, L. E., *J. Am. Chem. Soc.* **73**, 5471 (1951).

Leto, J. R., and Leto, M. F., *J. Am. Chem. Soc.* **83**, 2944 (1961).

Lewis, J. R., and Shoppee, C. W., *J. Chem. Soc.* p. 1365 (1955).

Lindlar, H., *Helv. Chim. Acta* **35**, 446 (1952).

Lutz, R. E., and Palmer, F. S., *J. Am. Chem. Soc.* **57**, 1957 (1935).

McQuillin, F. J., and Ord, W. O., *J. Chem. Soc.* p. 2902 (1959).

McQuillin, F. J., Ord, W. O., and Simpson, P. L., *J. Chem. Soc.* p. 5996 (1963).

Mancera, O., Ringold, H. J., Djerassi, C., Rosenkranz, G., and Sondheimer, F., *J. Am. Chem. Soc.* **75**, 1286 (1953).

Markgraf, J. H., Hess, B. A., Jr., Nichols, C. W., and King, R. W., *J. Org. Chem.* **29**, 1499 (1964).

Miropol'skaya, M. A., Fedotova, N. I., Veinberg, A. Ya., Yanotovskii, M. Ts., and Samokhvalov, G. I., *Zh. Obshch. Khim.* **32**, 2214 (1962).

Mitsuhashi, H., and Nagai, U., *Tetrahedron* **19**, 1277 (1963).

Montgomery, J. B., Hoffmann, A. N., Glasebrook, A. L., and Thigpen, J. I., *Ind. Eng. Chem.* **50**, 313 (1958).

Moore, W. R., *J. Am. Chem. Soc.* **84**, 3788 (1962).

Nair, M. D., and Adams, R., *J. Org. Chem.* **26**, 3059 (1961).

Nazarov, I. N., Ananchenko, S. N., and Torgov, I. V., *Zh. Obshch. Khim.* **26**, 1175 (1956).

Nes, W. R., *J. Am. Chem. Soc.* **78**, 193 (1956).

Newhall, W. F., *J. Org. Chem.* **23**, 1274 (1958).

Newman, M. S., and Addor, R. W., *J. Am. Chem. Soc.* **77**, 3789 (1955).

Nickon, A., and Bagli, J. F., *J. Am. Chem. Soc.* **83**, 1498 (1961).

Nomine, G., Bucourt, R., and Pierdet, A., U.S. Patent 3,115,507, Dec. 24, 1963.

Oliveto, E. P., Gerold, C., and Hershberg, E. B., *J. Am. Chem. Soc.* **74**, 2248 (1952).

Oshima, N., Sato, K., and Mitsui, S., *Nippon Kagaku Zasshi* **84** (2), 177 (1963).

Overberger, C. G., and Kabasakalian, P., *J. Am. Chem. Soc.* **79**, 3182 (1957).

Pachter, I. J., Raffauf, R. F., Ullyot, G. E., and Ribeiro, O., *J. Am. Chem. Soc.* **82**, 5187 (1960).

Parham, W. E., and Groen, S. H., *J. Org. Chem.* **29**, 2214 (1964).

Phillips, A. P., and Mentha, J., *J. Am. Chem. Soc.* **78**, 140 (1956).

Phillipps, G. H., U.S. Patent 3,115,508, Dec. 24, 1963.

Plattner, P. A., and Lemay, L., *Helv. Chim. Acta* **23**, 897 (1940).

Plattner, P. A., and Magyar, G., *Helv. Chim. Acta* **25**, 581 (1942).

Rapoport, H., Allen, R. H., and Cisney, M. E., *J. Am. Chem. Soc.* **77**, 670 (1955).

Ringold, H. J., *J. Am. Chem. Soc.* **82**, 961 (1960).

Roberts, J. D., Lee, C. C., and Saunders, W. H., Jr., *J. Am. Chem. Soc.* **76**, 4501 (1954).

Rodd, E. H., "Chemistry of Carbon Compounds," Vol. IVB, p. 841. Elsevier, Amsterdam, 1959.

Romilly, L. E., U.S. Patent 2,532,312, Dec. 5, 1950.

Roy, S. K., and Wheeler, D. M. S., *J. Chem. Soc.* p. 2155 (1963).

Rylander, P. N., and Karpenko, I., Unpublished work, Engelhard Ind., 1961.

Rylander, P. N., Himelstein, N., and Kilroy, M., *Engelhard Ind. Tech. Bull.* **4**, 49 (1963).

Sanchez-Viesca, F., and Romo, J., *Tetrahedron* **19**, 1285 (1963).

Sauvage, J. F., Baker, R. H., and Hussey, A. S., *J. Am. Chem. Soc.* **83**, 3874 (1961).

Schneider, H. J., Bagnell, J. J., and Murdock, G. C., *J. Org. Chem.* **26**, 1987 (1961).

Sengupta, P., and Khastgir, H. N., *Tetrahedron* **19**, 123 (1963).

Shepherd, D. A., Donia, R. A., Campbell, J. A., Johnson, B. A., Holysz, R. P., Slomp, G., Jr., Stafford, J. E., Pederson, R. L., and Ott, A. C., *J. Am. Chem. Soc.* **77**, 1212 (1955).

Shoppee, C. W., Agashe, B. D., and Summers, G. H. R., *J. Chem. Soc.* p. 3107 (1957).

Siegel, S., *Advan. Catalysis* **16**, 123 (1966).

Siegel, S., and Dmuchovsky, B., *J. Am. Chem. Soc.* **84**, 3132 (1962).

Siegel, S., and Smith, G. V., *J. Am. Chem. Soc.* **82**, 6082 (1960a).

Siegel, S., and Smith, G. V., *J. Am. Chem. Soc.* **82**, 6087 (1960b).

Slomp, G., Jr., Shealy, Y. F., Johnson, J. L., Donia, R. A., Johnson, B. A., Holysz, R. P., Pederson, R. L., Jensen, A. O., and Ott, A. C., *J. Am. Chem. Soc.* **77**, 1216 (1955).

Smith, G. V., and Burwell, R. L., Jr., *J. Am. Chem. Soc.* **84**, 925 (1962).

Smith, G. V., and Roth, J. A., *Proc. 3rd Intern. Congr. Catalysis, Amsterdam, 1964* Vol. 1,
    p. 379. North Holland Publ. Amsterdam 1965.
Smith, H. A., Fuzek, J. F., and Meriwether, H. T., *J. Am. Chem. Soc.* **71**, 3765 (1949).
Sorkin, E., Krähenbühl, W., and Erlenmeyer, H., *Helv. Chim. Acta* **31**, 65 (1948).
Sowden, J. C., and Fischer, H. O. L., *J. Am. Chem. Soc.* **69**, 1048 (1947).
Stevens, K. L., Lundin, R. E., and Teranishi, R., *J. Org. Chem.* **30**, 1690 (1965).
Stork, G., and Hill, R. K., *J. Am. Chem. Soc.* **79**, 495 (1957).
Stork, G., and Schulenberg, J. W., *J. Am. Chem. Soc.* **84**, 284 (1962).
Takimoto, H. H., Denault, G. C., and Krbechek, L. O., *J. Org. Chem.* **29**, 1899 (1964).
Tallent, W. H., *Tetrahedron* **20**, 1781 (1964).
Tarbell, D. S., Carman, R. M., Chapman, D. D., Cremer, S. E., Cross, A. D., Huffman, K. R.,
    Kunstmann, M., McCorkindale, N. J., McNally, J. G., Jr., Rosowsky, A., Varino, F. H. L.,
    and West, R. L., *J. Am. Chem. Soc.* **83**, 3096 (1961).
Taub, W., and Szmuszkovicz, J., *J. Am. Chem. Soc.* **74**, 2117 (1952).
Tepenitsyna, E. P., Farberov, M. I., and Dorogova, N. K., *Neftekhimiya* **3**(6), 876 (1963).
van Tamelen, E. E., and Proost, W. C., Jr., *J. Am. Chem. Soc.* **76**, 3632 (1954).
Vavon, G., *Compt. Rend.* **152**, 1675 (1911).
Webb, R. L., and Bain, J. P., *J. Am. Chem. Soc.* **75**, 4279 (1953).
Weidlich, H. A., and Meyer-Delius, M., *Chem. Ber.* **74B**, 1195 (1941).
Wenkert, E., and Jackson, B. G., *J. Am. Chem. Soc.* **81**, 5601 (1959).
Westman, T. L., and Kober, A. E., *J. Org. Chem.* **29**, 2448 (1964).
Weygand, C., and Meusel, W., *Chem. Ber.* **76B**, 498 (1943).
Whitehead, C. W., Traverso, J. J., Sullivan, H. R., and Marshall, F. J., *J. Org. Chem.* **26**,
    2814 (1961).
Wilds, A. L., Johnson, J. A., Jr., and Sutton, R. E., *J. Am. Chem. Soc.* **72**, 5524 (1950).
Woodward, R. B., Sondheimer, F., Taub, D., Heusler, K., and McLamore, W. M., *J. Am.
    Chem. Soc.* **74**, 4223 (1952).
Yashin, R., Rosenkranz, G., and Djerassi, C., *J. Am. Chem. Soc.* **73**, 4654 (1951).
Young, W. G., Meier, R. L., Vinograd, J., Bollinger, H., Kaplan, L., and Linden, S. L., *J. Am.
    Chem. Soc.* **69**, 2046 (1947).
Yurashevskii, N. K., *J. Gen. Chem. USSR (English Transl.)* **8**, 438 (1938).
Zajcew, M., *J. Am. Oil Chemists' Soc.* **37**, 11 (1960a).
Zajcew, M., *J. Am. Oil Chemists' Soc.* **37**, 473 (1960b).
Zimmerman, H. E., *J. Am. Chem. Soc.* **78**, 1168 (1956).

6

Imines

Hydrogenation of imines to amines usually proceeds readily over platinum metal catalysts:

$$-\overset{|}{C}=N- + H_2 \longrightarrow -\overset{|}{C}H-NH-$$
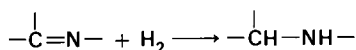
Successful reductions have been carried out over palladium, platinum, and rhodium catalysts in neutral, acidic, and basic media. Imines may be inter-mediates in reductive alkylation of amines with aldehydes or ketones, but are usually not isolated (Emerson, 1948). As a method of preparing amines, isolation and catalytic hydrogenation of imines may not prove so convenient as direct reductive alkylation of a carbonyl compound and amine (Layer, 1963), a reaction discussed at length in Chapter 16.

$$RCHO + R'NH_2 \longrightarrow [RCH=NR'] \overset{H_2}{\longrightarrow} RCH_2NHR'$$

Imines have been assumed to be intermediates in an interesting type of coupling reaction. Hydrogenation of benzylamine in ethanol over palladium gave an almost quantitative yield of dibenzylamine; β-phenylethylamine, similarly treated, gave only 10% of the corresponding secondary amine. The coupling reaction is assumed to proceed through dehydrogenation to the imine (Kindler et al., 1931).

$$2 \left\langle \bigcirc \right\rangle -CH_2NH_2 \overset{H_2}{\longrightarrow} (\left\langle \bigcirc \right\rangle -CH_2)_2NH + NH_3$$
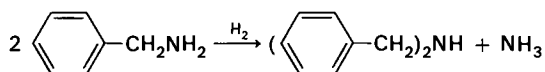
I. ACIDIC MEDIA

The saturated amines formed in hydrogenation of imines are compounds of a type known to act as inhibitors in catalytic reductions (Maxted and Walker, 1948; Maxted and Biggs, 1957; Breitner et al., 1959). To counteract the inhibiting effect of the product, reductions are sometimes carried out in

acidic media. Freifelder (1961), using benzylidenebutylamine as a model, showed that in reductions in 95% ethanol–5% methanol over rhodium the rate may be increased 5–8-fold by addition of certain acids. Tartaric, salicylic, phthalic, mandelic, and formic acids all had strong promoting action; cinchomeronic, p-toluenesulfonylacetic, and malonic acids were ineffective.

Acetic acid is a convenient solvent for carrying out imine hydrogenations. For instance, a series of imines derived from β-phenylethylamine and substituted benzaldehydes was readily reduced over platinum oxide in acetic acid (Buck, 1931). In another study, a series of benzylalkylamines was prepared by hydrogenating the corresponding Schiff base over platinum oxide in acetic acid at room temperature. The reductions were rapid and complete. These amines were prepared as intermediates in a sequence leading to dialkylamines. The benzylalkylamine was alkylated to give a tertiary amine, from which a pure secondary amine could be obtained by debenzylation over platinum oxide or palladium-on-carbon in acetic acid at 45 psig and 65–75°C (Buck and Baltzly, 1941).

$$C_6H_5CH{=}NR \xrightarrow{H_2} C_6H_5CH_2NHR \longrightarrow C_6H_5CH_2NRR' \xrightarrow{H_2} NHRR' + C_6H_5CH_3$$
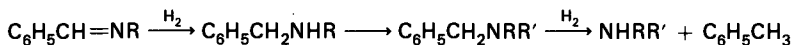
II. NEUTRAL OR BASIC MEDIA

Hydrogenation of imines is frequently carried out in neutral solvents, which include methanol, ethanol, dioxane, tetrahydrofuran, and ethyl acetate (Burke et al., 1955). Absolute ethyl alcohol containing a small amount of the original primary amine was the preferred solvent for reduction of a series of aliphatic imines to secondary amines. In this work, prereduced platinum oxide gave better yields of secondary amine than palladium-on-carbon; Raney nickel catalysts produced very little of the secondary amine (Campbell et al., 1944). In a typical reduction, 0.20 gm platinum oxide in 50 ml absolute ethanol was shaken with hydrogen at 25 psig for 10 minutes. After releasing the hydrogen, 0.28 mole of freshly distilled butylidene-propylamine in 50 ml absolute alcohol containing 3 ml propylamine was added to the catalyst mixture. Absorption of hydrogen ceased in 40 minutes under 50 psig initial pressure and propylbutylamine was isolated, after distillation, in 65% yield (Campbell et al., 1944).

A series of N-substituted diamines was prepared by reducing diimines over platinum oxide. The diimines, prepared by condensation of aldehydes or ketones with hexamethylenediamine, were for the most part reduced without solvent at 55 psig over prereduced platinum oxide. In some reactions small amounts of ethanol were added to assure homogeneity of the undried dialdimine layer (Wittbecker et al., 1947). Another worker from the same company carried out the reductions at 7500–10,000 psig (Brooks, 1947).

Imines hydrogenated in the presence of ammonia or an amine may undergo an exchange reaction that results in a mixture of products. The exchange is thought to precede reduction (Sekiya et al., 1963).

$$ArCH{=}NR + R'NH_2 \longrightarrow ArCH_2NHR' + RNH_2$$

III. EFFECT OF STRUCTURE

The rate of hydrogenation and sometimes the products depend on the structure of the imine. Roe and Montgomery (1953) reduced twenty-four derivatives of benzalaniline over platinum oxide in ethanol. The rates varied over a 10-fold range depending on the substituents in a manner that, as might be expected, could not be related to the Hammett equation (Hammett, 1940). Nitro functions were reduced concomitantly with the imine. Carbethoxy and cyano substituents caused marked decreases in rate of hydrogenation, whereas halogen substituents generally accelerated the rate. The authors comment that during this study three different batches of platinum oxide (Adams et al., 1946) were prepared, but no appreciable differences in activity of the three batches could be detected.

An attempt has been made to use the rate of hydrogenation over palladium-on-carbon to distinguish oxazolidines and the isomeric Schiff bases. The model substrates were I, II, and III. The Schiff base (I) showed no tendency to isomerize to a cyclic structure and the oxazolidines, due to the presence of the methyl group at the nitrogen atom, cannot exist in an open form. Contrary to expectations, the hydrogenolysis of the oxazolidines and hydrogenation of the Schiff base proceeded at roughly the same rates (Gil-Av, 1952).

(I)   (II)   (III)
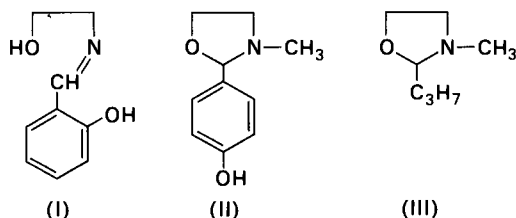
The results obtained in hydrogenation of the similar cyclic imines (IV and V) are interesting in that the course of reduction is unique to each, although both contain a tetrasubstituted carbon–carbon double bond in conjugation with the imine. By proper choice of solvent, the tetrasubstituted olefinic double bond in IV was selectively hydrogenated in the presence of the imine function (Meyers and Ritter, 1958). Only one equivalent of hydrogen was absorbed with reduction of the olefin over platinum oxide in anhydrous methanol, and two equivalents with reduction of both functions in acetic acid.

(IV)
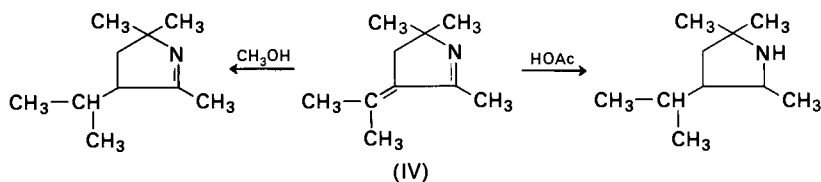
In contrast to the above, the similarly constituted molecule (V) absorbed one equivalent of hydrogen over platinum oxide in methanol, as if by 1,4-addition, to give VI. In acetic acid both centers of unsaturation were removed and two isomeric compounds were formed in a 50:1 ratio (Meyers *et al.*, 1963).

(V)   (VI)
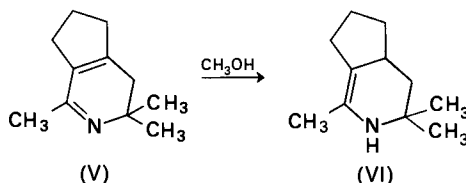
Suitably structured imines may undergo aromatization on reduction. Hydrogenation of the quinone imide (VII) over platinum oxide in methanol resulted in the aromatic compound (VIII) (Adams *et al.*, 1953):

(VII) R = *o*-tolyl   (VIII)
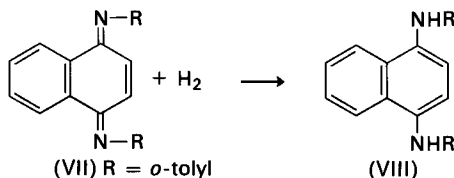
A similar reduction of 1,2-naphthoquinonedibenzenesulfonimide led to naphthylene-1,2-dibenzenesulfonamide (Adams and Wankel, 1951).

A. Steric Effects

Hydrogenation of imines will not occur easily if substituents in the neighborhood of the function block access to the catalyst. For instance, in a series of ketimines prepared by the action of Grignard reagents on *o*-tolunitrile, the relative rates of hydrogenation of IX were (R = methyl) 5.97,

(IX)
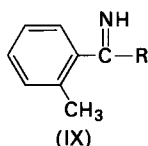
(ethyl) 3.32, (n-propyl) 2.64, (n-butyl) 2.36, (isobutyl) 1.54, (isoamyl) 1.47, and (sec-butyl) 1.00 (Pickard and Jenkins, 1953). The reductions were carried out over prereduced platinum oxide in absolute ethanol.

N-Substituted salicylideneimines and their Cu(II), Co(II), and Co(III) metal complexes were reduced over platinum oxide in alcohol. Reduction of the metal complexes was slow, as the metals tended to poison the catalyst. Quadridentate complexes were not reduced at all since they could not be accommodated on the catalyst surface (Beretka et al., 1964).

A preferential approach of the catalyst to one side of an imine will result in stereospecific reductions. Optically active N-methylbenzylidene-α-methyl-benzylamine (X) (21 gm) was rapidly reduced over 0.5 gm 10% palladium-on-carbon in 100 ml tetrahydrofuran to afford the saturated amine in 96% yield. The reduction proceeded with a high degree of stereospecificity, which the authors accounted for by assuming preferential hydrogenation of one isomer in a very facile equilibrium between the syn and anti forms of the imine:

anti   syn
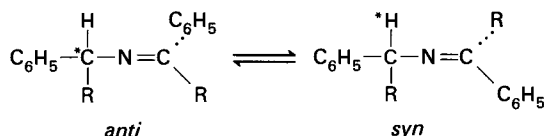
(X) R = CH$_3$ (XI) R = C$_2$H$_5$

Catalytic reduction of the more stable anti isomer proceeding from the least hindered side would give the meso-amine; reduction of the syn isomer would give the optically active amine. The authors suggested that the syn isomer, being a higher energy state, is more easily reduced, accounting for the observed generation of a new optically active center (Overberger et al., 1961). Hydrogenation of 10 gm optically inactive N-(1-phenylpropyl)-1-phenyl-propylideneimine (XI) over 200 mg platinum oxide in 200 ml ethanol afforded two optical forms of di(1-phenylpropyl)amine (Pohland and Sullivan, 1953).

B. Hydrogenolysis

Benzylamines undergo hydrogenolysis over platinum metal catalysts (Hartung and Simonoff, 1953), so it is to be expected that hydrogenolysis of the carbon–nitrogen bond is a side-reaction that may accompany reduction of imines derived from aromatic aldehydes. For instance, on catalytic
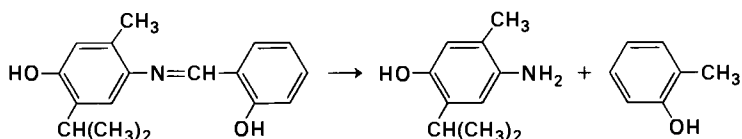
reduction over platinum, 2-hydroxybenzylidene-4-aminothymol underwent extensive hydrogenolysis and *p*-aminothymol was isolated as the hydrochloride in 70% yield (Sumerford *et al.*, 1940). It is not clear from the description of the experiment whether an effort was made to limit the absorption of hydrogen to one equivalent.

Similarly, imines derived from amino sugars and aromatic aldehydes undergo hydrogenolysis over palladium hydroxide-on-barium sulfate and reform the amino sugar (Kuhn *et al.*, 1961). Also, as noted before, hydrogenolysis of benzylamines derived by reduction of imines followed by alkylation has been used as a method for preparation of secondary amines (Buck and Baltzly, 1941).

Hydrogenolysis of the nitrogen–carbon bond is not confined to benzyl groups. An unusual and perhaps unique hydrogenolysis was discovered on reduction of the methiodide of the 3,4-dimethoxybenzylidene-2-(3,4-dimethoxyphenyl)ethylamine (XII) over platinum oxide in dioxane. Not only was the double bond reduced, but the *N*-methyl was also unexpectedly eliminated (Forbes, 1955).

(XII)
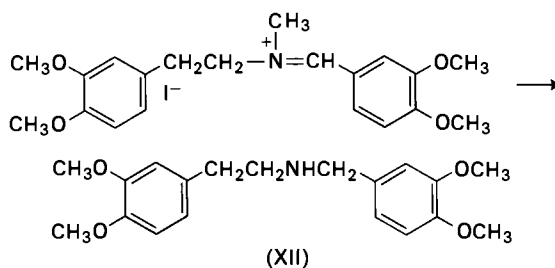
C. SELECTIVE HYDROGENATION

The number of imines, containing other reducible functional groups, that have been hydrogenated is quite small, making it difficult to generalize about selective hydrogenation of imines. Generalities concerning selectivity applicable to reductive alkylation are probably applicable also to hydrogenation of imines to the extent that imines are intermediates in reductive alkylation. It appears that imines are reduced fairly readily and that most functional groups, except the most easily reduced, will survive the reduction. Nitro groups are reduced prior to or concomitantly with imines (Roe and Montgomery, 1953). Imines frequently appear on partial hydrogenation of nitriles, which suggests that the nitrile group in an imine nitrile may not survive hydrogenation of the imine. The olefinic function in an unsaturated imine will usually be reduced preferentially, unless the substrate has some special structural features (Meyers *et al.*, 1963). Hydrogenation of imines

containing the cyclopropyl group has been carried out, leaving the cyclopropyl ring intact. *N*-Benzylidenecyclopropylamine (XIII) was readily reduced over 5% palladium-on-carbon in ethanol to give *N*-benzylcyclopropylamine (Horrom and Martin, 1963):

(XIII)
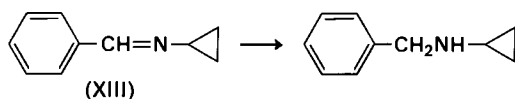
A similar compound, *trans-N*-(β-methylphenethyl)-2-phenylcyclopropylamine (XIV) was reduced over platinum oxide in ethanol (Kaiser and Zirkle, 1963).

(XIV)
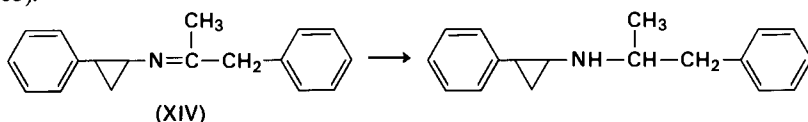
Dibenzylidene ethylenediamine (XV) in methanol was reduced at 50 psig and 30–45°C over 5% palladium-on-alumina. A 10% catalyst loading based on substrate was used in this reduction (Parker, 1958). The corresponding dichloro derivative (XVI) was reduced rapidly over platinum oxide in absolute ethanol at 45 psig without loss of the halogen. No comparison was made with another catalyst in this paper, but in all probability palladium would not have proved as effective as platinum and would have caused some hydrogenolysis of the halogen (Billman *et al.*, 1957).

(XV) R = H
(XVI) R = Cl

The lactam, 7-chloro-5-phenyl-(3H)1,4-benzodiazepin-2(1H)-one (XVII), was converted in high yield to the corresponding dihydro compound through reduction over platinum oxide in acetic acid. The corresponding nitrogen

(XVII)

oxide (XVIII) was similarly reduced with preservation of the halogen and reduction of the oxygen function to a hydroxylamine (Sternbach and Reeder, 1961):

(XVIII)

REFERENCES

Adams, R., and Wankel, R. A., *J. Am. Chem. Soc.* **73**, 2219 (1951).

Adams, R., Voorhees, V., and Shriner, R. L., *in* "Organic Syntheses," (Gilman, H. and Blatt, A. H., eds.). Wiley, New York, 1946. Collected Vol. I, p. 463.

Adams, R., Braun, B. H., and Pomerantz, S. H., *J. Am. Chem. Soc.* **75**, 4642 (1953).

Beretka, J., West, B. O., and O'Connor, M. J., *Australian J. Chem.* **17**(2), 192 (1964).

Billman, J. H., Ho, J.-Y. C., and Caswell, L. R., *J. Org. Chem.* **22**, 538 (1957).

Breitner, E., Roginski, E., and Rylander, P. N., *J. Chem. Soc.* p. 2918 (1959).

Brooks, R. E., U.S. Patent 2,416,042, Feb. 18, 1947.

Buck, J. S., *J. Am. Chem. Soc.* **53**, 2192 (1931).

Buck, J. S., and Baltzly, R., *J. Am. Chem. Soc.* **63**, 1964 (1941).

Burke, W. J., Adams, L. G., Murdock, K. C., and Ruetman, S. H., *J. Am. Chem. Soc.* **77**, 5637 (1955).

Campbell, K. N., Sommers, A. H., and Campbell, B. K., *J. Am. Chem. Soc.* **66**, 82 (1944).

Emerson, W. S., *Org. Reactions* **4**, 174 (1948).

Forbes, E. J., *J. Chem. Soc.* p. 3926 (1955).

Freifelder, M., *J. Org. Chem.* **26**, 1835 (1961).

Gil-Av, E., *J. Am. Chem. Soc.* **74**, 1346 (1952).

Hammett, L. P., "Physical Organic Chemistry," p. 186. McGraw-Hill, New York, 1940.

Hartung, W. H., and Simonoff, R., *Org. Reactions* **7**, 263 (1953).

Horrom, B. W., and Martin, W. B., U.S. Patent 3,083,226, Mar. 26, 1963.

Kaiser, C., and Zirkle, C. L., U.S. Patent 3,106,578, Oct. 8, 1963.

Kindler, K., Peschke, W., and Dehn, W., *Ann. Chem. Liebigs* **485**, 113 (1931).

Kuhn, R., Haas, H. J., and Seeliger, A., *Chem. Ber.* **94**, 1259 (1961).

Layer, R. W., *Chem. Rev.* **63**, 489 (1963).

Maxted, E. B., and Biggs, M. S., *J. Chem. Soc.* p. 3844 (1957).

Maxted, E. B., and Walker, A. G., *J. Chem. Soc.* p. 1093 (1948).

Meyers, A. I., and Ritter, J. J., *J. Org. Chem.* **23**, 1918 (1958).

Meyers, A. I., Schneller, J., and Ralhan, N. K., *J. Org. Chem.* **28**, 2944 (1963).

Overberger, C. G., Marullo, N. P., and Hiskey, R. G., *J. Am. Chem. Soc.* **83**, 1374 (1961).

Parker, G., U.S. Patent 2,862,969, Dec. 2, 1958.

Pickard, P. L., and Jenkins, S. H., Jr., *J. Am. Chem. Soc.* **75**, 5899 (1953).

Pohland, A., and Sullivan, H. R., *J. Am. Chem. Soc.* **75**, 5898 (1953).

Roe, A., and Montgomery, J. A., *J. Am. Chem. Soc.* **75**, 910 (1953).

Sekiya, M., Hara, A., and Masui, T., *Chem. Pharm. Bull. (Tokyo)* **11**, 277 (1963).

Sternbach, L. H., and Reeder, E., *J. Org. Chem.* **26**, 4936 (1961).

Sumerford, W. T., Hartung, W. H., and Jenkins, G. L., *J. Am. Chem. Soc.* **62**, 2082 (1940).

Wittbecker, E. L., Houtz, R. C., and Watkins, W. W., *J. Am. Chem. Soc.* **69**, 579 (1947).

7

Azines

Azines may be reduced over platinum metal catalysts to the disubstituted hydrazines and, if the reduction is continued, to the amine (Maihle, 1920). The reduction has been little studied and no comparison of the relative merits of various platinum metals has been made. Early workers (Lochte *et al.*, 1921) used colloidal platinum stabilized by gum arabic, but this type of catalyst has been largely replaced by platinum oxide.

I. SOLVENTS

Acids solutions are usually used in hydrogenation of azines. During early investigations on reduction of dimethylketazine to diisopropylhydrazine, it was found that continuous neutralization of the resulting hydrazine by hydrochloric acid gave vastly improved rates of hydrogenation. Later it was found more convenient to add the theoretical amount of hydrochloric acid at the beginning of the reduction. A further improvement consisted in carrying out the reduction on a mixture of one mole of hydrazine hydrate, one mole of hydrochloric acid, and two moles of acetone, obviating the isolation of the ketazine (Lochte *et al.*, 1921). Ugryumov (1940) observed that reduction of azines over platinum black proceeded more rapidly in acetic acid than in alcohol and very slowly in ether. Acetic acid is usually employed as a solvent.

II. PREPARATION OF AZO COMPOUNDS

A general method for preparation of azo compounds involves hydrogenation of an azine to a hydrazine, followed by oxidation of the product. Most reductions of azines seem to have been carried out for this purpose.

$$\begin{array}{c}
\diagdown \\
\diagup
\end{array}C{=}N{-}N{=}C\begin{array}{c}\diagup \\ \diagdown\end{array} \xrightarrow{\text{H}_2} \begin{array}{c}\diagdown \\ \diagup\end{array}CH{-}NH{-}NH{-}CH\begin{array}{c}\diagup \\ \diagdown\end{array} \xrightarrow{[O]} \begin{array}{c}\diagdown \\ \diagup\end{array}CH{-}N{=}N{-}CH\begin{array}{c}\diagup \\ \diagdown\end{array}$$
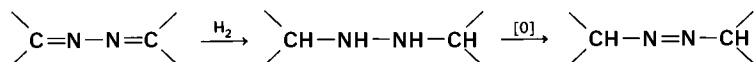
The azo compound may be obtained with or without isolation of the intermediate hydrazine. The azo compound (II) was obtained in 60% overall yield by hydrogenation of 6.2 gm 5-methoxy-1-indanone azine (I) over 0.3 gm platinum oxide in 15 ml acetic acid and 85 ml methanol, followed by air oxidation of the filtered solution. The hydrogenation was very slow and required 53 hours for completion (Panetta and Bunce, 1961).
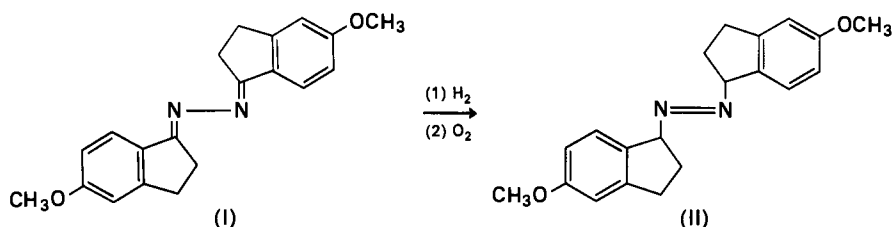
Reduction and subsequent oxidation of camphor azine afforded 2-azobornane in 76% overall yield. A mixture of 30 gm camphor azine and 100 ml acetic acid, hydrogenated over 0.3 gm platinum oxide, absorbed two equivalents of hydrogen in 12 hours whereupon absorption ceased spontaneously. The resulting 2-hydrazobornane was isolated and oxidized by potassium permanganate in acetone to 2-azobornane. The azo compound was also obtained by hydrogenation of camphor 2-bornylhydrazone in acetic acid over platinum oxide and subsequent oxidation (Berson *et al.*, 1962). A series of azo compounds was prepared by hydrogenation of azines (III) to hydrazines (IV) followed by oxidation of the crude product. The reductions, which became slower after absorption of two equivalents of hydrogen, were carried out over platinum oxide in acetic acid at 30 psig (Cohen *et al.*, 1950).
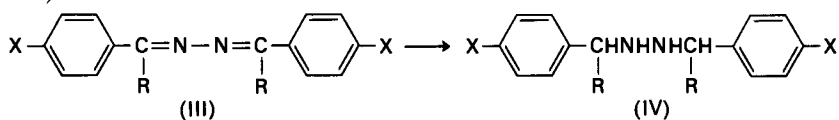
$R = CH_3, C_2H_5, (CH_3)_2CHCH_2$
$X = H, CH_3, CH_3O, Cl, C_6H_5$

Highly specific reaction conditions were necessary to obtain satisfactory hydrogenation of 3-(p-methoxyphenyl)-3-methyl-2-butanone azine (V). The reduction was moderated by the presence of ethyl acetate, which presumably prevented overhydrogenation. Hydrogenation was carried out with 1.52 gm
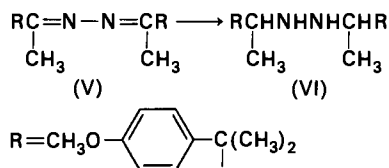
V in 10 ml ethyl acetate and 33 ml acetic acid over 150 mg platinum oxide. The azo compound was obtained by oxidation of the hydrogenation product (VI) with hydrogen peroxide (Overberger and Gainer, 1958).

REFERENCES

Berson, J. A., Olsen, C. J., and Walia, J. S., *J. Am. Chem. Soc.* **84**, 3337 (1962).
Cohen, S. G., Groszos, S. J., and Sparrow, D. B., *J. Am. Chem. Soc.* **72**, 3947 (1950).
Lochte, H. L., Bailey, J. R., and Noyes, W. A., *J. Am. Chem. Soc.* **43**, 2597 (1921).
Maihle, A., *Compt. Rend.* **170**, 1265 (1920).
Overberger, C. G., and Gainer, H., *J. Am. Chem. Soc.* **80**, 4556 (1958).
Panetta, C. A., and Bunce, S. C., *J. Org. Chem.* **26**, 4859 (1961).
Ugryumov, P. G., *J. Gen. Chem. USSR (English Transl.)* **20**(22), 1985, 1995 (1940).

8

Hydrazones

Hydrazones may be reduced over platinum metal catalysts to the corresponding hydrazines and, if the reduction is continued, to ammonia and the amine:

$$RCH=N-NH_2 \xrightarrow{H_2} RCH_2NHNH_2 \xrightarrow{H_2} RCH_2NH_2 + NH_3$$

Reductions of hydrazones may be complicated by disproportionation reactions leading to azines and their hydrogenation and hydrogenolysis products:

$$2RCH=N-NH_2 \longrightarrow RCH=N-N=CHR \longrightarrow RCH_2NH-NHCH_2R \longrightarrow 2RCH_2NH_2$$
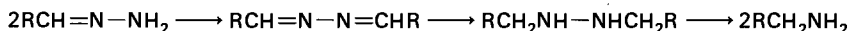
Some form of platinum catalyst has been used in most hydrogenations of hydrazones. Early workers used colloidal platinum stabilized by gum arabic (Poth and Bailey, 1923; Goodwin and Bailey, 1925), but this type of catalyst has been largely superseded by platinum oxide or platinum-on-carbon. Very little work using other platinum metals has been reported.

I. HYDROGENOLYSIS

Hydrazines vary in ease of hydrogenolysis, and satisfactory yields of easily reduced hydrazines may be obtained only with difficulty from certain hydrazones. For instance, catalytic hydrogenation of the hydrazone (I) over palladium or platinum oxide invariably resulted in hydrogenolysis with the formation of low boiling amines (Biel *et al.*, 1959a). Catalytic hydrogenation of the hydrazones (II) over platinum oxide in methanol afforded the hydrazines (III) when R = CH_3, C_2H_5, or C_3H_7, but when R = H or

$$\text{(I)} \quad \begin{array}{c} \overset{N}{\underset{CH_3}{\bigcirc}}\!\!-CH_2NHN=CHCH_2N(CH_3)_2 \end{array}$$

134
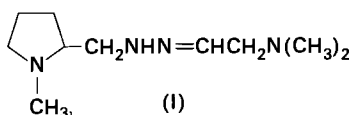
C_6H_5 hydrogenolysis occurred (Schulze and Letsch, 1963). In general, hydrogenolysis of the nitrogen–nitrogen bond is a likely side-reaction in the reduction of hydrazones, and the possibility is always present that the yield of hydrazine will be diminished if reductions are not interrupted after absorption of one equivalent of hydrogen. Continued reduction may afford excellent yields of amines (Overberger and Gainer, 1958). Hydrogenolysis

$$(ClCH_2CH_2)_2NN\!=\!\underset{\underset{R}{|}}{C}\!-\!COOH \qquad\qquad (ClCH_2CH_2)_2NNH\underset{\underset{R}{|}}{C}HCOOH$$

$$\qquad\qquad (II) \qquad\qquad\qquad\qquad\qquad\qquad (III)$$

of hydrazones may prove in certain circumstances superior to reductive amination for conversion of carbonyl compounds to the amine, inasmuch as disubstituted amines are unlikely to be formed in hydrazone reductions.

Quantitative hydrogenolysis reactions proved invaluable in elucidation of the structure of the antibiotic elaiomycin (IV). This aliphatic α,β-unsaturated azoxy compound absorbed two equivalents of hydrogen when reduced over prereduced platinum oxide in absolute ethanol to give the hydrazone, deoxydihydroelaiomycin (V). On further reduction of V in acetic acid–acetic anhydride over platinum oxide, two more equivalents of hydrogen were absorbed to give a mixture of amines. Two hydrogenolysis reactions were indicated by absorption of these four equivalents of hydrogen (Stevens et al., 1958).

$$n C_6H_{13}CH\!=\!CH\!-\!\overset{\overset{O}{\uparrow}}{N}\!=\!N\!-\!\underset{\underset{\underset{CH_3}{|}}{\overset{|}{CHOH}}}{\overset{|}{CH}}\overset{\overset{CH_2OCH_3}{|}}{} \longrightarrow n C_6H_{13}CH_2CH\!=\!NNH\underset{\underset{\underset{CH_3}{|}}{\overset{|}{CHOH}}}{\overset{|}{C}H}\overset{\overset{CH_2OCH_3}{|}}{}$$

$$\qquad (IV) \qquad\qquad\qquad\qquad\qquad\qquad (V)$$

$$\qquad\qquad\qquad\qquad \overset{CH_2OCH_3}{}\;\Big\downarrow Ac_2O$$

$$CH_3\underset{\underset{O}{\|}}{C}NH\!-\!\underset{\underset{\underset{CH_3}{|}}{\overset{|}{CHOCOCH_3}}}{\overset{\overset{CH_2OCH_3}{|}}{C}H}$$
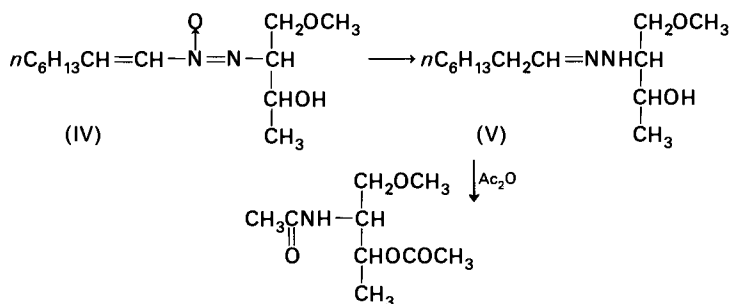
II. DISPROPORTIONATION

With certain hydrazones, disproportionation to azines occurs readily and competes with hydrogenation of the hydrazone. In this circumstance the products of hydrogenation may vary markedly with the conditions of reduction in an understandable way. The reduction of 1-phenyl-2-propyl hydrazone (VI) is illustrative of the effect of reaction conditions on product composition. Reduction of this substrate gave the hydrazine (VII), the azine (VIII), the symmetrical hydrazine (IX), and the amine (X) in ratios that depended on the conditions of the reduction. Large amounts of the azine

(VIII) were obtained when the reduction went slowly and incompletely, as with palladium-on-carbon, rhodium, ruthenium, or platinum oxide in alcohol, water, ethyl acetate, tetrahydrofuran, or dioxane. Slow reductions, such as those with platinum oxide in acetic acid, that tended more toward completion gave chiefly the symmetrical hydrazine (IX). Reductions over Raney nickel in ethanol gave almost exclusively a mixture of azine (VIII) and amine (X). Acceptable yields of the asymmetrical hydrazine (VII) were obtained when the hydrogenation was carried out rapidly so that competing disproportionation reactions were minimized. For instance, 741 gm phenylacetone hydrazone (5.0 moles) in 900 ml absolute ethanol and 300 gm acetic acid (5.0 moles) reduced over 10 gm platinum oxide at 1875 psig afforded 1-phenyl-2-propylhydrazine (VII) in 68 % yield (Biel et al., 1959b).

$$RC=N-NH_2 \longrightarrow RCHNHNH_2 + RC=N-N=CR +$$
$$\quad | \qquad\qquad\qquad\qquad | \qquad\qquad | \qquad\quad |$$
$$CH_3 \qquad\qquad\qquad CH_3 \qquad\quad CH_3 \qquad CH_3$$

<div align="center">(VI)   (VII)   (VIII)</div>

$$R = C_6H_5CH_2 \qquad RCHNHNHCHR + RCHNH_2$$
$$\qquad\qquad\qquad\qquad | \qquad\quad | \qquad\quad |$$
$$\qquad\qquad\qquad\quad CH_3 \quad CH_3 \quad CH_3$$

<div align="center">(IX)   (X)</div>
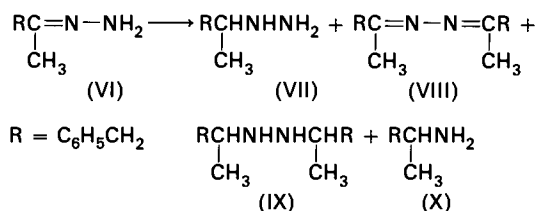
The high pressures used for satisfactory reduction of VI to VII are unnecessary when the substrate is so constituted that competing disproportionation reactions occur at a relatively slow rate. For instance, 52 gm benzylacetone hydrazone (0.32 mole) in 250 ml alcohol and 19.3 gm acetic acid (0.32 mole), reduced over 0.5 gm platinum oxide at 60 psig, afforded 1-phenyl-3-hydrazinebutane in 73 % yield (Biel et al., 1959b).

$$RCH_2C=N-NH_2 \longrightarrow RCH_2CH-NH-NH_2$$
$$\qquad | \qquad\qquad\qquad\qquad\qquad |$$
$$\qquad CH_3 \qquad\qquad\qquad\qquad CH_3$$

$$R = C_6H_5CH_2$$
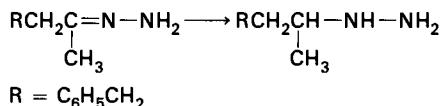
Troublesome disproportionation reactions of hydrazones may be circumvented by carrying out the reduction on a derivative of the hydrazone. Hydrogenation of triphenylacetaldehyde hydrazone to triphenylethylhydrazine was unsuccessful because of the tendency of the substrate to be converted to azine. However, the acetylhydrazone of triphenylacetaldehyde was easily reduced and hydrolyzed to the hydrazine. The hydrogenation, carried out over platinum oxide in acetic acid, gave the acetylhydrazine in 97.8 % yield (Curtin and Miller, 1960).

$$(\phi)_3C-CH=N-NHCCH_3 \xrightarrow[\text{(2) H}_2\text{O}]{\text{(1) H}_2} (\phi)_3CCH_2NHNH_2$$
$$\qquad\qquad\qquad\qquad\quad \| $$
$$\qquad\qquad\qquad\qquad\quad O$$
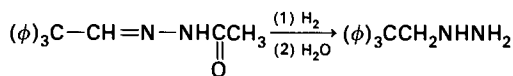
Cycloheptylhydrazine was conveniently prepared through hydrogenation of ethyl 3-cycloheptylidenecarbazate and subsequent basic hydrolysis.

The hydrogenation, carried out over 5% platinum-on-carbon in absolute ethanol, gave ethyl 3-cycloheptylcarbazate in 91% yield. Cycloheptyl-hydrazine could not be prepared by reduction of cycloheptylidenehydrazine over platinum oxide; only the unchanged hydrazone and dicycloheptylidene-hydrazine (68%) could be isolated after a very slow reduction (Cinnamon and Weiss, 1961). The marked difference in ease with which the carbazate and the hydrazone were hydrogenated is probably a reflection of the relative basicity of the nitrogen in these compounds and its inhibiting effect on the catalyst. The use of these derivatives also tends to minimize nitrogen–nitrogen bond hydrogenolysis. It has been pointed out that resistance to hydrogenolysis is a characteristic of semicarbazide structure. Carbo-hydrazide was reduced in 8 hours to semicarbazide over Raney nickel, but in an additional 24 hours no further hydrogen was absorbed (Corwin and Reinheimer, 1951).

$$H_2 + H_2N-NH-CO-NH-NH_2 \longrightarrow H_2N-NH-CO-NH_2 + NH_3$$
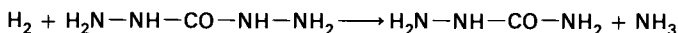
An interesting paper on techniques of reduction of 1-halobenzoyl-2-isopropylidenehydrazines has been published by Freifelder et al. (1961):
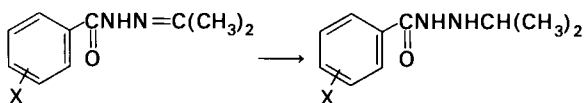
Reduction of the nitrogen–carbon double bond occurred readily over platinum, a catalyst that proved much superior to palladium in allowing hydrogenation without dehydrohalogenation. 1-p-Chlorobenzoyl-2-iso-propylidenehydrazine, 20 gm in 250 ml 95% ethanol, reduced over 1.5 gm 5% platinum-on-carbon at 2 atm. afforded the corresponding hydrazine in 94% yield. Theoretical hydrogen was absorbed within an hour, and no further absorption occurred. The extent of dehydrohalogenation accompany-ing the reduction was found to vary directly with the amount of catalyst. By operating at low catalyst loading levels even the labile bromo compounds could be reduced with very little dehydrobromination.

III. HYDRAZINES BY REDUCTIVE ALKYLATION

Hydrazines may be formed directly from a carbonyl compound by re-ductive alkylation without isolation of an intermediate hydrazone. For instance, substituted acid hydrazides of the general formula RCONHNHR' were prepared by hydrogenation of an acid hydrazide over platinum oxide in the presence of a carbonyl compound, such as benzaldehyde (Gutmann et al., 1961) or N-methyl-4-piperidone (Jucker et al., 1959). Alkyl hydrazines

are formed by reductive alkylation of hydrazine; hydrazine hydrate and methyl isobutyl ketone in hydrochloric acid, reduced over platinum oxide at 25°C and 1500 psig, were converted to 2-methylpentyl-4-hydrazine (British Patent 870,581).

REFERENCES

Biel, J. H., Hoya, W. K., and Leiser, H. A., *J. Am. Chem. Soc.* **81**, 2527 (1959a).

Biel, J. H., Drukker, A. E., Mitchell, T. F., Sprengler, E. P., Nuhfer, P. A., Conway, A. C., and Horita, A., *J. Am. Chem. Soc.* **81**, 2805 (1959b).

Cinnamon, J. M., and Weiss, K., *J. Org. Chem.* **26**, 2644 (1961).

Corwin, A. H., and Reinheimer, J. D., *J. Am. Chem. Soc.* **73**, 1184 (1951).

Curtin, D. Y., and Miller, T. C., *J. Org. Chem.* **25**, 885 (1960).

Freifelder, M., Martin, W. B., Stone, G. R., and Coffin, E. L., *J. Org. Chem.* **26**, 383 (1961).

Goodwin, R. C., and Bailey, J. R., *J. Am. Chem. Soc.* **47**, 167 (1925).

Gutmann, H., Straub, O., and Zeller, P., U.S. Patent 2,970,159, Jan. 31, 1961.

Jucker, E., Rissi, E., Suess, R., Vogel, A., and Wolff, E., U.S. Patent 2,883,389, Apr. 21, 1959.

Overberger, C. G., and Gainer, H., *J. Am. Chem. Soc.* **80**, 4556 (1958).

Poth, E. J., and Bailey, J. R., *J. Am. Chem. Soc.* **45**, 3001 (1923).

Schulze, W. and Letsch, G., *J. Prakt. Chem.* **21**, (5–6), 272 (1963).

Stevens, C. L., Gillis, B. T., French, J. C., and Haskell, T. H., *J. Am. Chem. Soc.* **80**, 6088 (1958).

9

Oximes

Catalytic hydrogenation of oximes may give primary amines,

$$RCH{=}NOH + 2H_2 \longrightarrow RCH_2NH_2 + H_2O$$

secondary or tertiary amines,

$$2RCH{=}NOH + 4H_2 \longrightarrow (RCH_2)_2NH + 2H_2O + NH_3$$
$$3RCH{=}NOH + 6H_2 \longrightarrow (RCH_2)_3N + 3H_2O + 2NH_3$$
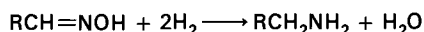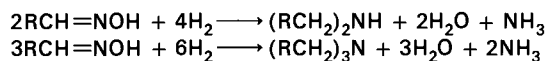
or alcohols derived by reductive hydrolysis,

$$RCH{=}NOH + 2H_2 \longrightarrow RCH_2OH + NH_3$$
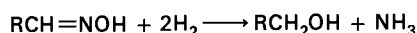
and under certain conditions intermediate hydrogenation products may be formed,

$$RCH{=}NOH + H_2 \longrightarrow RCH_2NHOH$$
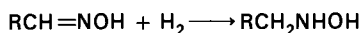
Various other products derived by interaction with the solvent and with other functional groups may arise. The fate of other reducible functions, the most common of which is the ketonic group, is a problem of frequent concern in hydrogenation of oximes. Oximino ketones, because of their availability and the value of their reduction products in medicine, have been the subject of extensive study.

The course of oxime hydrogenation appears to be unusually sensitive to the catalyst, substrate, and reaction environment, making generalization about these reductions particularly tenuous. In the sections that follow, various effects of catalyst, solvent, and substrate on the course of reduction are described, as well as some factors involved in formation of partially reduced, coupled, and rearranged products.

I. CATALYSTS

The very few studies comparing the hydrogenation of oximes over various platinum metal catalysts indicate that the catalyst is of unusual influence

in determining the course of reduction. A comparison of palladium, platinum, rhodium, and ruthenium in hydrogenation of acetoxime and 3-pentanone oxime has been made (Rylander and Steele, 1965), with the results shown in Table I. The hydrogenations were conducted without solvent, as this condition tends to maximize coupling reactions and to emphasize differences among the catalysts. Of these metals, rhodium gave the best yield of primary amine. The trend found in these experiments parallels examples from the literature. Low yields of primary amine by hydrogenation of oximes over palladium or platinum in nonacidic media have frequently been obtained; on the other hand, rhodium has given excellent yields of primary amine (Freifelder et al., 1962).

TABLE I
HYDROGENATION OF OXIMES: EFFECT OF METAL[a]

Hydrogenation of acetoxime			
Catalyst (300 mg)	Temperature (°C)	Isopropylamine (% by wt.)	Diisopropylamine (% by wt.)
5% Pd/C	100	14	ca. 86[c]
5% Pt/C	75–100[b]	32	ca. 68[c]
5% Rh/C	77	65	ca. 35[c]
5% Ru/C	76–100[b]	—	90% isopropanol

Hydrogenation of 3-pentanone oxime					
Catalyst[d] (500 mg)	Temperature (°C)	1° Amine (% by wt.)	2° Amine (% by wt.)	Pentanol (% by wt.)	Pentanone (% by wt.)
5% Pt/C	100	30	0	7	ca. 63
5% Rh/C	78	50	0	5	45
5% Ru/C[e]	100	17	0	ca. 83	ca. 0

[a] Pressure 1000 psig, substrate 12.5 gm.
[b] The reductions were begun at the lower temperature and the temperature was increased when absorption proved too slow.
[c] Small amounts of alcohol and ketone were present.
[d] 5% Pd/C was rapidly poisoned in reduction of 3-pentanone oxime.
[e] 5 ml H_2O added; without H_2O reduction was too slow.

Another comparison of catalysts has been made in hydrogenation of 2-indanone oxime. Reduction of this substrate in acetic acid–sulfuric acid over 5% palladium-on-carbon gave 2-aminoindane in 90–95% yield, over 5% platinum-on-carbon gave 2-(hydroxylamino)indane in 54% yield, and over 5% rhodium-on-carbon no absorption of hydrogen took place (Rosen and Green, 1963). One might have anticipated that the most 2-(hydroxylamino)-indane would have been formed over platinum, but the extreme variation in results shown here could hardly have been predicted.

The rate of hydrogenation of cyclohexanone oxime in various solvents over 5% palladium-, platinum-, rhodium-, and ruthenium-on-carbon has been measured. The effect of solvent is marked. Rhodium is particularly active in neutral or alkaline solution, platinum in acid solution. Palladium gives poor rates, and ruthenium shows good activity only in aqueous solution (Breitner *et al.*, 1959).

Rhodium has been used infrequently in hydrogenation of oximes, but apparently excellent results may be achieved. For instance, cycloheptylamine was obtained in 80% yield by hydrogenation of cycloheptanone oxime over 5% rhodium-on-carbon in methanol. The oxime, formed from cycloheptanone and hydroxylamine, was used directly without purification except for drying the oily oxime layer over anhydrous magnesium sulfate. This oily oxime, formed from 4000 gm cycloheptanone, was dissolved in 9000 ml methyl alcohol containing 450 gm 5% rhodium-on-alumina and reduced at 1 atm and 25–60°C until absorption stopped. After filtration and fractionation, cycloheptylamine was obtained in 80% overall yield based on cycloheptanone (Freifelder *et al.*, 1962).
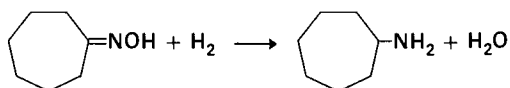
The sensitivity of certain oxime reductions to the catalyst is well illustrated in a paper entitled "Change in the behavior of palladium-on-charcoal in hydrogenation reactions." The authors (Hartung and Chang, 1952) noted that during the 18 years they had worked with palladium catalysts a qualitative change in behavior had developed. For example, whereas previously α-oximino ketones on absorption of two moles of hydrogen afforded practically pure amino ketone, they now gave about equal amounts of a mixture of amino alcohol and oximino alcohol. They attributed this change to trace amounts of impurities in the earlier samples of palladium chloride from which the catalyst was made. In fact, when about 1.5% based on palladium of other platinum metals was added to the later samples of palladium chloride, the character of the reduction changed. The addition of iridium had adverse effects, ruthenium gave inconclusive results, but platinum or rhodium produced results approximating those obtained earlier. When these catalysts were reused the products were different from those obtained with fresh catalysts. The reduction, of α-oximinopropiophenone is also very sensitive to the way in which the palladium catalysts are prepared (Karpenko, 1958). Improved results in this reduction have been obtained by using palladium and platinum catalysts together (Wilbert and Sosis, 1962). A mixture of catalysts, such that the palladium is 30–70% of the total metal and the platinum is 70–30%, gives excellent yields of product and the catalysts can be reused repeatedly without adverse effect on the product quality. The rate of

hydrogenation with these two catalysts together is considerably greater than that found with either alone, with the total weight of metal held constant (Karpenko, 1958).

II. SUBSTRATE

The products obtained in hydrogenation of oximes are the resultant of several competing reactions, each of which depends in part on the structure of the substrate. Reductive coupling reactions leading to secondary amines are evidently very sensitive to steric effects. The amount of secondary amine decreases as the bulk of the substituents in the vicinity of the oxime increases. Large amounts of dialkylamines were obtained in hydrogenation of ace-toxime, whereas under the same conditions 3-pentanone oxime afforded no dialkylamine (Table I). Similar results were found by others (Dornow and Frese, 1952). Only oximes of methyl ketones gave primary and secondary amines in hydrogenation over platinum oxide in methanol; ketoximes with longer chains gave primary amines only. An exception to this generality was found in the branched compound, $C_6H_5CH=CCH_3C(NOH)CH_3$, which gave only primary amine.

Oximes of simple cyclic ketones may form predominantly secondary amines on hydrogenation. Catalytic hydrogenation of 3-methylcyclo-hexanone oxime over platinum in acetic acid gave almost exclusively bis(3-methylcyclohexyl)amine (Mousseron et al., 1947). About equal weights of primary and secondary amines were obtained together with 3-methyl-cyclohexanol and 3-methylcyclohexanone when the reduction was carried out over platinum oxide in methanol (Hückel and Thomas, 1961). Hydro-genation of cyclopentanone oxime over platinum oxide gave dicyclopentyl-amine in 80% yield. When the reduction was carried out over platinum oxide in ethanol saturated with ammonia, dicyclopentylamine was still formed in yields of up to 71% together with cyclopentanol (Hückel and Kupka, 1956). These results stand in sharp contrast to the low tendency of the open-chain analog, 3-pentanone oxime, to form secondary amines.

The presence of a bulky substituent adjacent to the oxime in a cyclic ketone will tend to decrease secondary amine formation. Hydrogenation of 2-phenylcyclohexanone oxime over platinum oxide in acetic acid gave a mixture of trans- and cis-1-amino-2-phenylcyclohexanes in 1:2 ratio (Masamune et al., 1964).

trans: cis =1:2
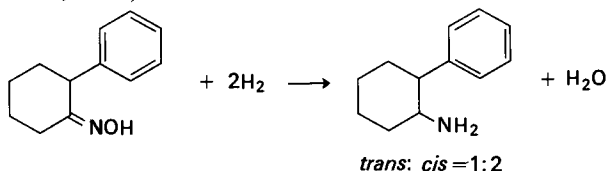
When oximes interact during catalytic hydrogenation, they usually do so in such a way that a new carbon–nitrogen bond is formed to afford ultimately a secondary amine or tertiary amine. In certain circumstances the interaction may proceed so that a new carbon–carbon bond is formed. A case in point is the reduction of the dioxime of 3,3,7,7-tetracarbethoxycyclooctane-1,5-dione (I) over 10%. palladium-on-carbon in ethanol–hydrogen chloride. The bicyclic diamine (II) was obtained in 73 % yield (Cope and Kagen, 1958). The authors suggest that the product has the *cis* configuration on the grounds that the *cis*-bicyclo[3.3.0]octane ring is more stable than the corresponding *trans* structure, and by analogy to the course followed in hydrogenation of the corresponding diketone, which gave the bridged glycol of *cis* configuration.

(I) R = —COOEt   (II) R = —COOEt
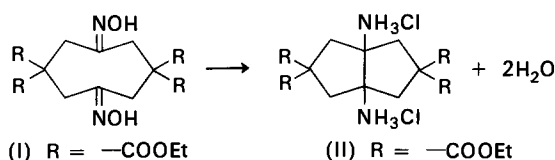
Reduction of oxime acetates may proceed quite differently than that of the free oxime. For instance, reduction of benzaldehyde oxime in ethanol gave considerable dibenzylamine, in acetic acid less was formed, and, if the oxime were first acetylated with acetic anhydride and pyridine, a high yield of benzylamine was obtained over a palladium-on-barium sulfate catalyst (Rosenmund and Pfannkuch, 1923).

III. SOLVENT

The products from hydrogenation of oximes depend to an unusual degree on the solvent employed. Hydrogenation of oximes in neutral media usually leads to mixtures of primary, secondary, and tertiary amines. Paal and Gerum (1908) reduced benzaldoxime in aqueous alcohol over colloidal palladium and obtained a mixture of benzylamine and dibenzylamine. The same mixture was obtained by hydrogenation of benzonitrile, which led the authors to postulate benzylideneimine as a common intermediate in reduction of these substrates. Hartung (1928) was the first to realize that formation of secondary amines could be prevented by carrying out the hydrogenation in acidic media. Benzaldoxime dissolved in absolute ethanol containing three equivalents of hydrogen chloride was quantitatively converted to benzylamine hydrochloride by hydrogenation over palladium-on-carbon; if only one equivalent of hydrogen chloride were present, a mixture of benzyl and dibenzylamine resulted. Since this work, alcoholic hydrogen chloride has been used as a solvent with success by many other investigators for hydrogenation of oximes to primary amines. For instance,

reduction of imidazole-4-aldehyde oxime over 5% palladium-on-carbon in methanol containing dry hydrogen chloride was used to prepare a good quality 4-(aminomethyl)imidazole dihydrochloride after other methods had failed to give this compound in pure form (Turner *et al.*, 1949).
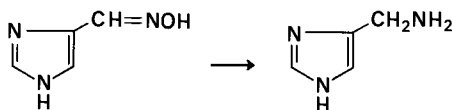
A number of other acidic media have been used for hydrogenation of oximes, including acetic acid, acetic acid containing hydrogen chloride, sulfuric, phosphoric, or perchloric acid, boron trifluoride, or zinc chloride–hydrogen chloride (Rosenmund *et al.*, 1942). Various acidic systems are not necessarily interchangeable. For instance, 2-indanone oxime could be reduced in ethanol–hydrogen chloride only if an especially active palladium-on-carbon catalyst were employed (Levin *et al.*, 1944), no absorption occurred in acetic acid–hydrogen chloride or in acetic acid–phosphoric acid, but excellent yields of 2-aminoindane were easily obtained in acetic acid–sulfuric acid (Rosen and Green, 1963).

Acid solutions are frequently used in hydrogenation of α-oximino ketones. Acid prevents the formation of dihydropyrazines and contaminating secondary and tertiary amines, and has a marked accelerating effect on the rate of hydrogenation. In neutral solution the rate is much lower, and the reduction does not usually cease spontaneously after absorption of one equivalent of hydrogen nor continue until three equivalents are absorbed. A mixture of products usually results. In alkaline solution excellent yields of amino alcohols have been obtained. For instance, 16.3 gm α-oximino-propiophenone in 100 ml 5% ethanolic sodium hydroxide was reduced over 2 gm palladium-on-carbon catalyst (prepared from palladium chloride and sodium acetate). The crude amino alcohol, norephedrine, was obtained in 80% yield, or 67% yield after recrystallization from benzene. A similar reduction of 1,3-diphenyl-2-oximino-1-propanone quantitatively afforded the corresponding amino alcohol (Hartung and Chang, 1952).

A. ACID ANHYDRIDE SOLVENTS

Oximes hydrogenated in acetic anhydride solvent are acetylated as they are reduced. The use of anhydride solvents may aid in isolation of the product and prevent interaction of the amine with other functional groups while the reduction is being completed. For instance, ethyl α-acetamido-acetoacetate was obtained in quantitative yield by reduction of the corresponding oxime over 5% palladium-on-carbon in acetic anhydride–acetic

acid solvent. Ethyl α-oximinoacetoacetate (0.1 mole) was dissolved in a mixture of 50 ml acetic anhydride and 150 ml acetic acid. Reduction of this mixture over 1 gm 5% palladium-on-carbon at 50 psig was complete in 90 minutes (Albertson *et al.*, 1948):

$$CH_3C-C-COOC_2H_5 \longrightarrow CH_3C-CHCOOC_2H_5$$
$$\quad \| \quad \| \qquad\qquad\qquad \| \quad |$$
$$\quad O \quad NOH \qquad\qquad\quad O \quad NHCOCH_3$$
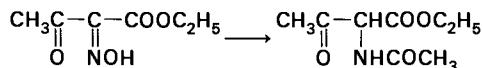
Similarly, 3-acetamido-2,4-pentanedione is formed in good yield by reduction of 3-oximino-2,4-pentanedione in acetic anhydride (Hoy and Hartung, 1958) over an acetate palladium-on-carbon catalyst with 100 mg palladium chloride per gm carrier (Cash *et al.*, 1956). Platinum oxide was used for hydrogenation in acetic anhydride of oximes derived from benzotropolones (Buchanan and Sutherland, 1957).

B. PRODUCTS OF HYDROLYSIS

Alcohols and ketones may arise in hydrogenation of oximes through competitive hydrolysis. In aqueous media and with certain catalysts in nonaqueous media, they may be the major products of reduction. A possible route to alcohols in reduction of oximes in aqueous media is through hydrolysis of the oxime followed by hydrogenation of the resulting ketone, but a more likely route is catalytic hydrogenolysis of the nitrogen–oxygen bond followed by hydrolysis of the resulting imine. It was found that the major product in hydrogenation of cyclohexanone oxime in water was cyclohexanol and not cyclohexylamine, but in the time required for complete hydrogenation no measurable amount of hydroxylamine, determined by titration, was formed by hydrolysis (Breitner *et al.*, 1959).
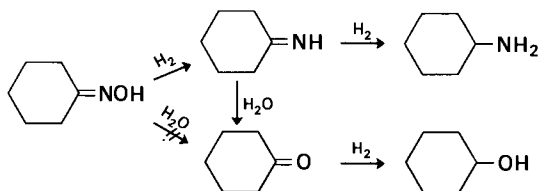
Hydrolysis of the imine is competitive with hydrogenation, and conditions that lessen the opportunity for hydrolysis should favor increased yields of amine. Table II shows the effect of various solvents on the yield of cyclohexylamine obtained in hydrogenation of cyclohexanone oxime over 5% rhodium-on-carbon. The yield of cyclohexylamine increased sharply when the reductions were carried out in the presence of ammonia. Ammonia has been used to increase the yield of primary amine at the expense of secondary amine (Reeve and Christian, 1956), but in this reduction its beneficial effect on yield seems to arise mostly from its competition with water in nucleophilic

TABLE II

HYDROGENATION OF CYCLOHEXANONE OXIME IN VARIOUS SOLVENTS[a]

Solvent	Solvent (ml)	Percent Yield of cyclohexylamine
Water	400	25
NaOH (0.125 M)	400	29
NH_3 (conc. aq.)	400	77
Methanol	100	48
Ethanol	100	55
Methanol (satd. with NH_3)	100	82

[a] Each experiment used 10 gm substrate, 5 gm 5% rhodium-on-carbon.

attack on the imine. The yield of secondary amine was in all experiments less than a few percent (Breitner et al., 1959).

Hydrolysis of an imine is also competitive with the addition of an amine to the imine to give ultimately a secondary amine. An inverse yield relationship may be expected between alcohols and secondary amines. For example, hydrogenation of acetoxime over palladium, platinum, and rhodium gave large percentages of diisopropylamine and a small percentage of acetone or isopropanol, while 3-pentanone oxime afforded no secondary amine and large percentages of pentanol and pentanone (Table I). The extremely large percentages of oxygenated products formed in reduction of these compounds over ruthenium is exceptional, and suggests that hydrogenation of oximes over ruthenium follows a course different from that over other metals. Ruthenium also gave appreciably more oxygenated products than rhodium in hydrogenation of the isomeric methylcyclohexanone oximes (Table III).

TABLE III

HYDROGENATION OF METHYLCYCLOHEXANONE OXIMES:
EFFECT OF METAL ON PRODUCT[a]

Catalyst (300 mg)	Oxime isomer	Rate (ml H_2/minute)	Percent trans-methylcyclohexylamine[b]	Percent methylcyclohexanol[c]
5% Rh/C	2	150	42	33
5% Ru/C	2	50	46	60
5% Rh/C	3	190	63	27
5% Ru/C	3	50	65	54
5% Rh/C	4	230	28	10
5% Ru/C	4	107	—	—[d]

[a] Temperature 100°C, pressure 1000 psig; solvent was water.
[b] Based on methylcyclohexylamine present.
[c] Based on C_7's present.
[d] Mostly alcohol and ketone.

Small percentages of bis(methylcyclohexyl)amines were also present but were not measured quantitatively. Secondary amines were the major product when these compounds were reduced over 5% palladium-on-carbon under the same conditions (Rylander and Steele, 1963).

C. ADDITION OF SOLVENT

A major by-product in the hydrogenation of 2-indanone oxime over palladium in methanol–hydrogen chloride is *trans*-2-amino-1-indanol. The reduction is believed to proceed through attack of methanol on 2-(hydroxyl-amino)indene, hydrolysis, and reduction (Rosen and Green, 1963). Support for this sequence was given by the observation that 2-amino-1-indanone was obtained in 50% yield when 2-indanone oxime was treated with methanol–hydrogen chloride without catalyst or hydrogen.
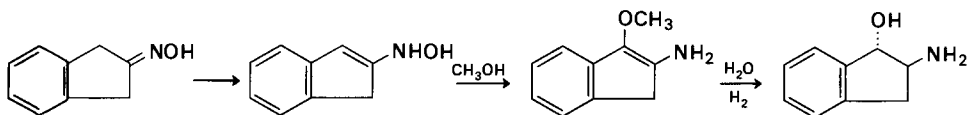
Formation of amino alcohols or ketones on hydrogenation of oximes is not general. Under the same conditions as above, 1-indanone oxime was reduced with difficulty and, except for unchanged substrate, only 1-indanone was identified (6–7% yield). Hydrogenation of 2-tetralone oxime gave 2-naphthylamine, rather than 2-amino-1-tetralone. The authors suggested that the 1-methoxy-2-imino stage, analogous to the path for 2-indanone oxime, may have been reached, but the driving force for aromatization resulted in elimination of methanol and formation of 2-naphthylamine.
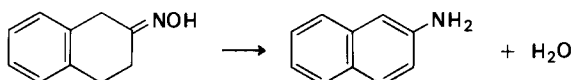
Catalytic hydrogenation of 3-acetonyloxindole oxime over platinum oxide in ethanolic hydrogen chloride proved to be unexpectedly complicated. The
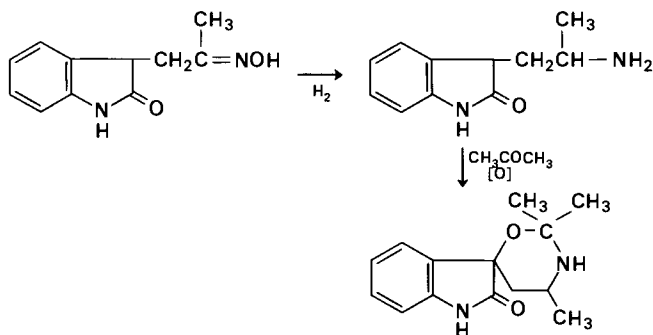
product obtained in 58% yield was derived through platinum-catalyzed oxidation of the intermediate and incorporation of the recrystallization solvent (Islip and White, 1964).

Oxindoles are readily oxidized at the 3-position, and colloidal platinum is known to effect the catalytic oxidation (Smidt et al., 1959). The yield of product was sensitive to the reduction pressure. At 50 psig, the absorption of two moles was rapid, and the final product was obtained in 58% yield; at atmospheric pressure the yield was less than 40%. A similar incorporation of the solvent occurred when the product was recrystallized from methyl ethyl ketone. These results stand in marked contrast to the hydrogenation of the similar compounds (III and IV) in 80% aqueous methanol over palladium-on-carbon. The reduction proceeded smoothly to oxindole-3-alanine (V), a compound obtained otherwise only with difficulty (Julian et al., 1956).
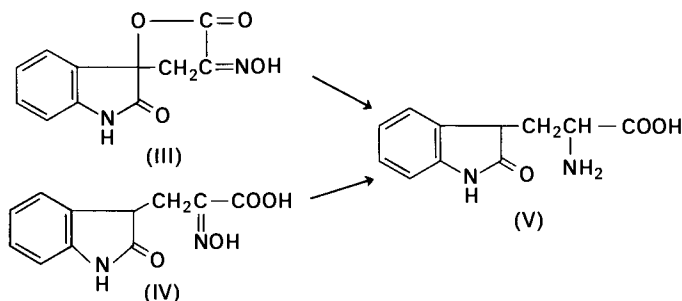
IV. PRODUCTS OF PARTIAL REDUCTION

Partial hydrogenation of an oxime may afford either a hydroxylamine or an imine. Imines are rarely obtained as products, inasmuch as they usually undergo further reduction to the amine, hydrolysis to a ketone, or coupling with an amine to give ultimately a secondary amine. Hydroxylamines, on the other hand, are reduced with more difficulty and are frequently found as a product of the reduction, especially if platinum catalysts are used. For instance, hydrogenation of 2-indanone oxime over 5% platinum-on-carbon in acetic acid–sulfuric acid gave 2-(hydroxylamino)indane in 54% yield. Under the same conditions hydrogenation over palladium-on-carbon gave 2-aminoindane in 90–95% yield. The authors suggested that in mineral acid solutions 2-(hydroxylamino)indene (VI) is a key intermediate, and that the products depend on the ratio of saturation of the carbon–carbon double bond to nitrogen–oxygen bond hydrogenolysis. The hydroxylaminoindane (VII) was shown not to be an intermediate in the formation of aminoindane (VIII) (Rosen and Green, 1963).
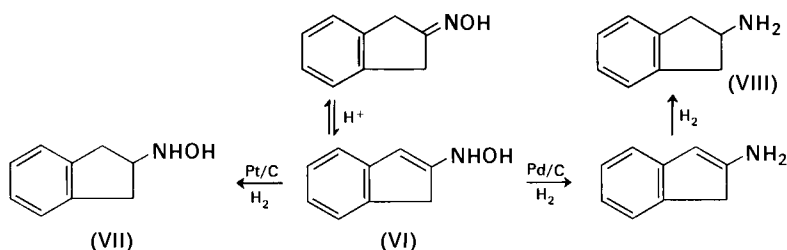
The authors noted that, although this role of acid and this sequence of reactions were suggested specifically for hydrogenation of 2-indanone oxime, it might have broader applicability. They pointed out, however, that mineral acid catalysis has also been observed in oximes not having a hydrogen on the α-carbon atom (Hartung, 1928). The authors also pointed out that, alternatively, platinum reductions in acid may involve direct hydrogenation of the carbon–nitrogen bond in indanone oxime to give hydroxylamino-indane directly.

Although hydroxylamino compounds may be reduced to the corresponding amine over platinum metal catalysts, they probably are not, as demonstrated specifically above, intermediates in the formation of amines by hydrogenation of oximes. Amines, it appears, result from hydrogenolysis of the nitrogen–oxygen bond while some unsaturation is still present. In a further example, α-hydroxylamino acids can be reduced slowly over palladium-on-carbon to the corresponding amino acid, but evidently are not intermediates in the formation of amino acids by hydrogenation of oximino acids. When the hydrogenation of α-oximino acids was interrupted after one equivalent of hydrogen had been taken up, the product was a mixture of α-amino acid and unchanged substrate (Neelakantan and Hartung, 1958). The goal, then, in obtaining hydroxylamino compounds from oximes lies not so much in preventing further reduction of the hydroxylamino function, but rather in expediting its formation initially.

Judging from rather limited literature, it appears that hydroxylamines are best formed in acidic solution over platinum catalysts. For instance, hydrogenation of 2-indanone oxime in anhydrous ethanol over platinum-on-carbon gave unchanged substrate and diindanylamine. In contrast to the neutral solution, reduction in methanol–hydrogen chloride gave no diindanylamine at all and 30–35 % 2-(hydroxylamino)indane. In acetic acid–sulfuric acid the yield of 2-(hydroxylamino)indane rose to 54%. In this acetic acid–sulfuric acid solvent, palladium-on-carbon gave high yields of 2-aminoindane, while no reduction at all occurred over 5 % rhodium-on-carbon (Rosen and Green, 1963). Several aliphatic hydroxylamines were formed by reduction of ketoximes over platinum black in ethanol–hydrogen chloride, but under the same conditions acetophenone oxime gave mainly

phenylethylamine (Vanon and Krajcinovic, 1928). Phenylacetoxime after absorption of one equivalent of hydrogen afforded N-(β-phenylisopropyl)-hydroxylamine in 42% yield (Gilsdorf and Nord, 1952). Hydrogenation of aldoximes in this system gave secondary hydroxylamines; benzaldoxime gave dibenzylhydroxylamine plus some dibenzylamine, isobutyraldehyde oxime gave diisobutylhydroxylamine, and piperonal oxime gave dipiperonyl-hydroxylamine (Vanon and Krajcinovic, 1928).

$$2RCH{=}NOH + 2H_2 \longrightarrow (RCH_2)_2NOH + NH_3$$

Reduction of 2,4-dimethoxyphenylacetaldehyde oxime over platinum oxide in ethanol containing oxalic acid gave a mixture of the oxalate of phenylethylamine and the neutral oxalate of the hydroxylamine derivative, $[(MeO)_2C_6H_3CH_2CH_2]_2NOH$ (Reichert and Koch, 1935).

Oximes need not be isolated before reduction to hydroxylamines. An aqueous emulsion of cycloheptanone or cyclooctanone (0.086 mole), when hydrogenated with 6.0 gm hydroxylamine hydrochloride over platinum oxide at 50°C, gave after neutralization 62% and 31% of the corresponding alicyclichydroxylamine (Müller et al., 1955).

Jones and Major (1930) reduced several O-alkyl-substituted oximes to the corresponding O,N-dialkylhydroxylamine hydrochlorides over platinum oxide in ethanol–hydrogen chloride:

$$R{-}\underset{\displaystyle R}{C}{=}NOR' \cdot HCl + H_2 \longrightarrow R{-}\underset{\displaystyle R}{CH}{-}NHOR' \cdot HCl$$
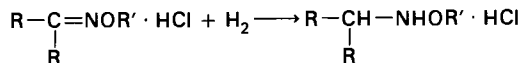
The reductions were always accompanied by formation of ketones, alcohols, and ammonium chloride. These side-reactions were most pronounced in reduction of methyl and ethyl acetoxime hydrochlorides, where about 75% of the reduction followed this course. Presumably these by-products arise from hydrolysis preceding complete hydrogenation. No hydroxylamine was obtained on reduction of O-methylbenzaldoxime; the products were benzyl- and dibenzylamines.

AROMATIZATION

Certain suitably structured alicyclic oximes may on reduction be converted to an aromatic amine. In a sense these amines are products of partial reduction, for the system is still unsaturated and could be further reduced.

$$\text{(IX)} + 4H_2 \longrightarrow \text{(X)} + 2H_2O$$
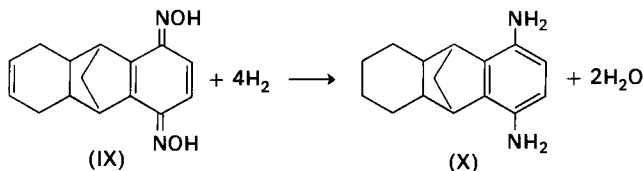
For example, the 1,4-dioxime (IX) was easily reduced over platinum oxide in methanol. Aromatization accompanied hydrogenation and the aromatic diamine (X), isolated as the hydrochloride, was obtained in 95% yield (Vaughan and Yoshimine, 1957). Similarly, hydrogenation (no hydrogen is actually absorbed) of 2-tetralone oxime afforded 2-naphthylamine (Rosen and Green, 1963).

V. OXIMINO KETONES

The first attempts to reduce aromatic oximino ketones resulted in mixtures of primary and secondary amines. Hartung and Munch (1929) were able to circumvent the formation of secondary amines by carrying out the reduction over a palladium-on-carbon catalyst in the presence of excess hydrogen chloride dissolved in ethanol. In the absence of hydrogen chloride, the ketone was reduced first; further hydrogenation reduced the oxime to the primary amine, contaminated with secondary and tertiary amines (Hartung, 1931).

The course of reduction of aromatic oximino ketones depends on the aromatic substituents. Aromatic oximino ketones, ArCOCR=NOH, in which the aromatic moiety is phenyl, *m*- or *p*-tolyl, or naphthyl, are reduced smoothly in absolute alcohol with three equivalents of hydrogen chloride to the amino alcohol over a palladium-on-carbon catalyst (Hartung and Munch, 1929; Hartung *et al.*, 1930, 1935). When the aromatic portion is a phenol or phenyl methyl ether, the reduction stops at the amino ketone stage (Hartung, 1931; Hartung *et al.*, 1931).

It appears that the major product of reduction of oximino ketones in acidic solution is, after absorption of two equivalents of hydrogen, always the amino ketone, although its yield may be quite sensitive to small changes in the catalyst (Hartung and Chang, 1952). Good yields of the amino ketone (XII) were obtained by reduction of the oximino ketone (XI) over platinum oxide in methanol-hydrochloric acid. The initial reduction was very rapid and isothermic. After 20 minutes the rate had fallen greatly and the reduction was stopped. The amino ketone hydrochloride was obtained in 78% yield after recrystallization. Further reduction of the amino ketone in methanol over platinum oxide gave stereoselectively an 84% yield of the β-phenanthrol (XIII) (Murphy, 1961).
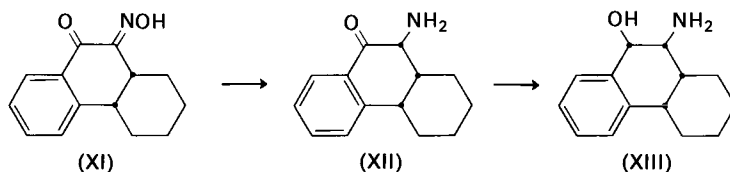
In hydrogenation of a related compound (XIV), a special technique was used to prepare the amino ketone (XV). The reduction was carried out in ethanol–hydrogen chloride over 10% palladium-on-carbon and the oxime was added in small portions, each new portion being added only after hydrogen uptake had ceased. The success of the technique implies that hydrogenation of the ketonic function is relatively very slow (Bien and Ginsburg, 1963).

(XIV)   (XV)
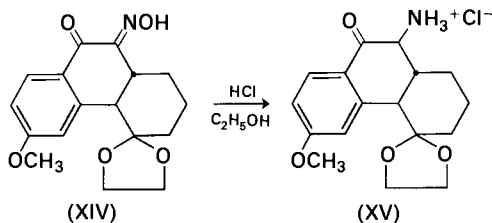
A route to imidazolones involves hydrogenation of α-oximino ketones. Oximinoacetone (XVI) and ethyl α-oximinoacetoacetate (XVII) were reduced to the corresponding amino ketones over 2.5% palladium-on-carbon in ethanol–hydrochloric acid. The amino ketones were not isolated but treated directly with potassium cyanate to afford the 4-methylimidazolones in 75% and 81% overall yields, respectively (Duschinsky and Dolan, 1945).

$$CH_3COCR{=}NOH \longrightarrow CH_3COCHRNH_2 \longrightarrow$$

(XVI)   R = H
(XVII)   R = $COOC_2H_5$
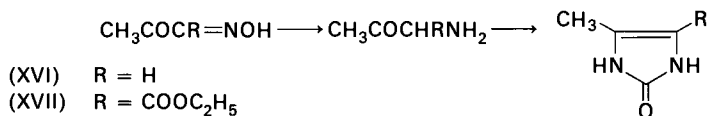
The presence of an additional ketonic function was found in one series to influence the course of reduction. Hydrogenation of XVIII (R = CH_3) over palladium oxide in ethanolic hydrogen chloride resulted in the amino alcohol (XIX). Further reduction over platinum oxide in 50% aqueous ethanol gave the amino diol (XX). When R = C_6H_5 (XXI), reduction over palladium oxide produced an appreciable quantity of XXII, in which hydrogenolysis of the benzyl hydroxyl had occurred. It would appear from these results considered together that the adjacent amino function can

(XIX) R = CH_3 (XX) R = CH_3

(XVIII) R = CH_3
(XXI)   R = C_6H_5

(XXII) R = C_6H_5
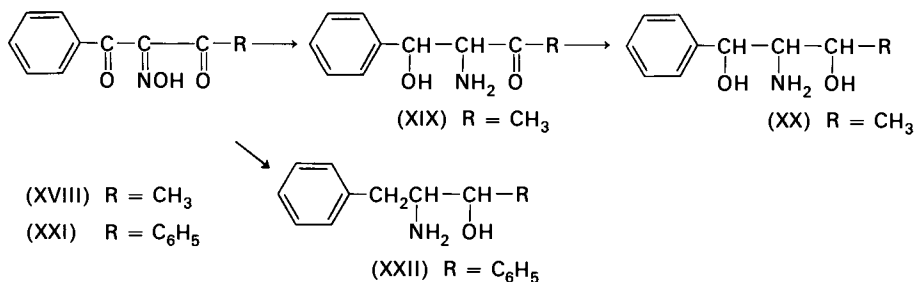
stabilize one benzyl hydroxyl group against hydrogenolysis, but not two (Rebstock, 1951).

Fairly vigorous conditions are sometimes required for reduction of amino ketones to the amino alcohols, as illustrated by the work of Meltzer and Lewis (1957). Hydrogenation of 0.38 mole of XXIII as the hydrochloride was carried out in 1 liter of absolute ethanol containing 1.15 moles of additional hydrogen chloride over 11 gm 10% palladium-on-carbon at 1000 psig. After absorption of two equivalents of hydrogen the amino ketone was isolated by evaporation of the solvent, but not purified. The residue was taken up in a liter of water and another 11 gm catalyst was added and the reduction continued at 1000 psig until another equivalent of hydrogen was absorbed. When the ring substituent was p-dimethylaminoethoxy, it was necessary to heat the second stage of the reduction to about 100°C to obtain a satisfactory rate. Both stages of the reduction required heating when the corresponding *ortho* isomer was reduced.
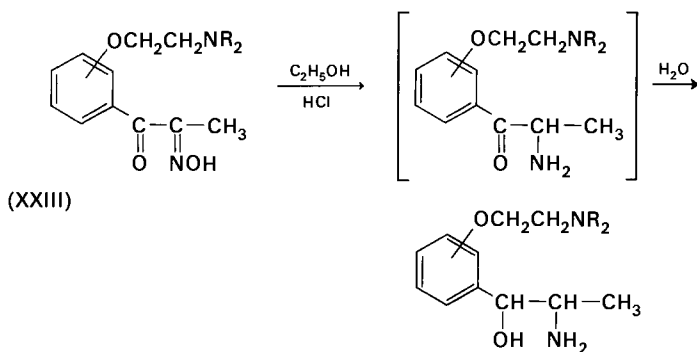
VI. PRODUCTS OF INTERACTION WITH OTHER FUNCTIONS

The products obtained by hydrogenation of oximes may be derived by interaction of the initially formed amine or hydroxylamine with other suitably situated functions. For instance, reduction of ethyl δ-amino-δ-(3,4-dimethoxyphenyl)valerate (XXIV) in acetic acid over 5% palladium-on-carbon gave the lactam (XXV) in 98% yield (Koo, 1953). A more complex example is the conversion of 3-acyloxindole oximes to 2-alkylindoles through interaction of an intermediate hydroxylamine with an amide. Catalytic hydrogenation of 3-acyloxindole oximes (XXVI) converts them to mixtures
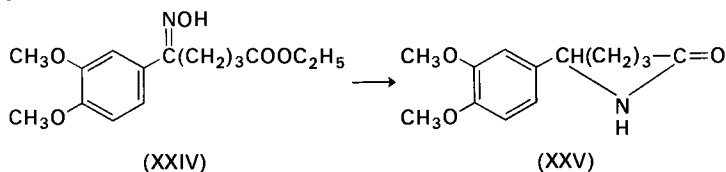
of 3-(α-aminoalkylidene)oxindoles (XXVII) and 2-alkylindoles (XXVIII) (Wenkert et al., 1958). The aminoalkylidene derivatives are tautomers of

(XXVI)   (66%) (XXVII)   (21%) (XXVIII)
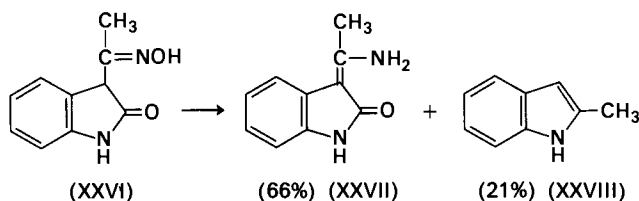
imines, which could be formed by direct hydrogenolysis of the nitrogen–oxygen bond and by elimination of water from the hydroxylamine inter-mediate. Formation of indoles involves an extensive rearrangement that, the authors suggest, proceeds through reduction of the oxime to the hydroxyl-amine (XXIX), rearrangement to the dihydroisooxazolone (XXX), decar-boxylation, and cyclization with loss of ammonia. In this work consistent results were obtained with palladium-on-carbon in ethanol, but erratic results were obtained with platinum in acetic acid.

(XXIX)   (XXX)
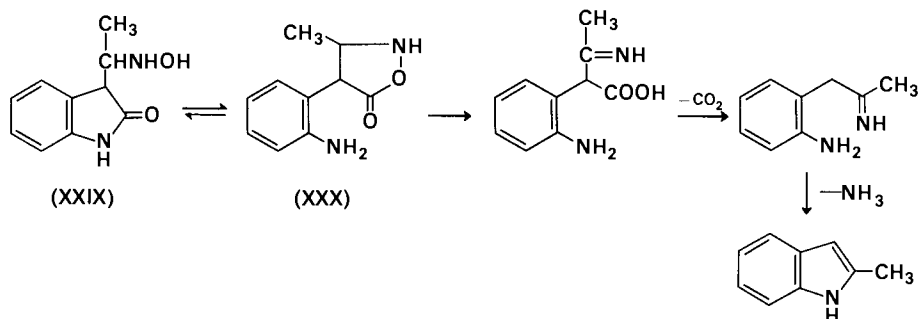
Hydrogenation of XXXI over platinum oxide in ethanol afforded none of the anticipated 1-amino-2-acetoxypyrroloindole. Instead two products were obtained, one of which arose by an acyl migration from oxygen to nitrogen (XXXII). The other product was assigned tentatively the oxazoline structure (XXXIII). The products were both presumed to have a *cis* configuration

(XXXI)

(XXXII)

(XXXIII)
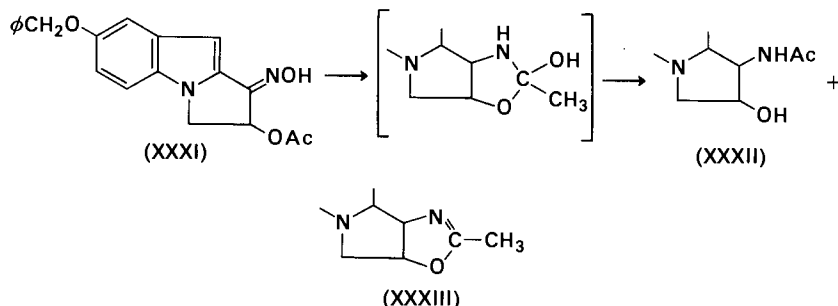
arising from a common cyclic intermediate. Platinum was used in this reduction to preserve the benzyloxy function, which was easily cleaved over palladium (Remers *et al.*, 1965).

The second reactive function need not necessarily be in the same molecule. Ochiai and Miyamoto (1937) obtained 2,4-dimethyl-3,5-diacetylpyrrole
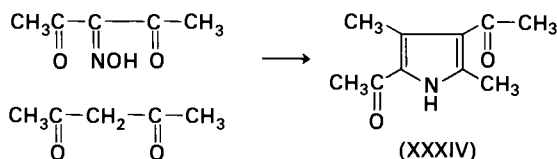
(XXXIV) in 75% yield by reduction of a mixture of one mole of isonitro-soacetylacetone and 1 mole of acetylacetone over 40% palladium-on-carbon in water. The yield is greater when the pH of the reaction medium is low. When benzene or acetic acid is used as a solvent, 2,5-dimethyl-3,6-diacetyl-pyrazine is formed, but no pyrrole.

VII. STEREOCHEMISTRY

An important factor in the stereochemistry of the hydrogenation of oximes is the presence of neighboring groups. Hydrogenation of α-oximino ketones usually gives the amino alcohol as a single racemic modification, although two diastereoisomeric racemates might be expected. For instance, reduction of benzoin oxime over 5% palladium-on-carbon in ethanol–hydrogen chloride gave nearly a quantitative yield of DL-*erythro*-α,β-diphenyl-β-hydroxyethylamine (Weijlard *et al.*, 1951). Chang and Hartung (1953), to account for these high stereospecificities, have suggested that the polar oxygen and nitrogen atoms of the substrate molecule adsorb on the catalyst to form a rigid ring-like structure. The same racemic modification would be formed whether the initial hydrogen addition to this structure was 1,4-followed by *cis*-addition of the second molecule of hydrogen, or 1,2- followed by 1,4-addition.

The stereochemistry of reduction of oximino ketones may be influenced by other neighboring groups. For instance, a novel route to DL-norephedrine involved catalytic hydrogenation of α-isonitroso-β-chloropropiophenone. The reduction, carried out in the presence of 30% palladium-on-carbon (Pfau and Plattner, 1940) in methanol–hydrogen chloride, gave norephedrine in 90% yield. The reduction followed a stereospecific course and the possible
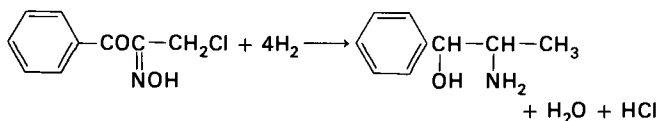
by-product, nor-ψ-ephedrine, could not be isolated. On the other hand, hydrogenation of the similar compound, α-isonitroso-β-ethoxypropio-phenone, did not follow a stereospecific course and a mixture of *threo* and *erythro* isomers resulted. (Matsumoto and Hata, 1957).

Hydroxyl groups adjacent to the oximino function also tend to direct the hydrogenation in such a way that the resulting amino function bears a *cis* relation to the hydroxyl. For example, hydrogenation of sebacoin oxime over rhodium-on-carbon in methanol gave the *cis* amino alcohol, obtained pure in 52 % yield by a single crystallization from petroleum ether (Fanta *et al.*, 1963). Reduction of D-fructose oxime over platinum oxide in acetic acid led stereospecifically to the D-mannitol derivative and not the D-glucitol. The compound isolated after acetylation was 2-acetamido-2-deoxy-D-mannitol. The authors presented the generality that reduction of hexose oximes over platinum in acid medium directs the new group to the *cis* position with respect to its immediate neighbor (Roth *et al.*, 1964).

Brimacombe and Cook (1964), working with amino sugars, have offered the generality, based on their own and other earlier results, that catalytic reduction of oximes or hydrazones attached to cyclohexane or pyranose rings usually leads to a preponderance of the epimer having an axial amino group in the stable chair form. For instance, reduction of the oxime of 6-deoxy-α-L-arabino-hexopyranuloside over platinum in butanol led to amino sugars with 2.4 parts of the *manno* epimer and 1 part of the *gluco* epimer. With less-flexible ring systems the higher yield of the amino sugars possessing an axial amino group is even more marked (Brimacombe and How, 1963). Amino sugars available otherwise only with difficulty may be obtained through reductions of this type.

EFFECT OF CATALYST OR SOLVENT

Very few investigations have compared the effect of various catalysts or solvents on the stereochemistry of hydrogenation of oximes. The percentages of *trans*-methylcyclohexylamine formed on reduction of 2-, 3-, and 4-methylcyclohexanone oximes over 5 % rhodium-on-carbon and 5 % ruthen-ium-on-carbon have been determined (Rylander and Steele, 1963); the results are shown in Table III. The percentage of *trans* isomer varies only slightly with the metal. The main differences between the catalysts are found in the rates of hydrogenation and in the extent of the competing hydrolysis reactions. These oximes were also reduced over 5 % palladium-on-carbon, affording in each case the bis(methylcyclohexyl)amine as the major product. The ratio of *cis-trans* isomers found in the methylcyclohexylamine may depend somewhat on the activity of the catalyst; hydrogenation of 2-methylcyclohexanone oxime in acetic acid over a highly active platinum

catalyst afforded only the *cis* isomer, whereas with a less active catalyst a mixture of *cis* and *trans* isomers was formed (Anziani and Cornubert, 1945).

The catalyst support may also influence the stereochemistry of hydrogenation, but no investigation of the effect of support seems to have been made. By using an asymmetric support, Akabori *et al.* (1956) were able to achieve an asymmetric reduction of oximes over a palladium-on-silk catalyst.

The effect of solvent on the stereochemistry of reduction over 5 % rhodium-on-carbon of 2-, 3-, and 4-methylcyclohexanone oximes has been determined (Rylander and Steele, 1963); the results are shown in Table IV. The solvent has some effect on the percentage of *trans* isomer found in the product, but the effect is relatively small compared to the effect that the substrate itself has. Substantial losses in yield of amine through competing hydrolysis reactions are suffered when aqueous solvents are used.

TABLE IV

HYDROGENATION OF METHYLCYCLOHEXANONE OXIMES: EFFECT OF SOLVENT[a]

Oxime isomers	Solvent	Rate (ml H_2/minute)	Percent *trans*-MCH–amine[b]	MCH alcohol[c]
2	Water	150	42	33
2	Ethanol	205	31	< 1
2	NH_3(conc.)	130	37	10
2	Cyclohexane	205	34	< 1
2	None	250	40	< 1
3	Water	190	63	27
3	Ethanol	180	70	0
3	Acetic acid	280	65	0
3	Cyclohexane	140	65	< 1
3	None	180	70	0
4	Water	230	28	10
4	Ethanol	—	28	0

[a] Temperature 100°C, pressure 1000 psig; catalyst, 300 mg 5% Rh/C.
[b] Based on methylcyclohexylamine present.
[c] Based on C_7's present.

REFERENCES

Akabori, S., Izumi, Y., Fujii, Y., and Sakurai, S., *Nippon Kagaku Zasshi* 77, 1374 (1956).
Albertson, N. F., Tullar, B. F., King, J. A., Fishburn, B. B., and Archer, S., *J. Am. Chem. Soc.* 70, 1150 (1948).
Anziani, P., and Cornubert, R., *Compt. Rend.* 221, 103 (1945).
Bien, S., and Ginsburg, D., *J. Chem. Soc.* p. 2065 (1963).
Breitner, E., Roginski, E., and Rylander, P. N., *J. Chem. Soc.* p. 2918 (1959).
Brimacombe, J. S., and Cook, M., *J. Chem. Soc.* p. 2663 (1964).
Brimacombe, J. S., and How, M. J., *J. Chem. Soc.* p. 3886 (1963).

Buchanan, G. L., and Sutherland, J. K., *J. Chem. Soc.* p. 2334 (1957).

Cash, W. D., Semeniuk, F. T., and Hartung, W. H., *J. Org. Chem.* **21**, 999 (1956).

Chang, Y.-T., and Hartung, W. H., *J. Am. Chem. Soc.* **75**, 89 (1953).

Cope, A. C., and Kagen, F., *J. Am. Chem. Soc.* **80**, 5499 (1958).

Dornow, A., and Frese, A., *Arch. Pharm.* **285**, 463 (1952).

Duschinsky, R., and Dolan, L. A., *J. Am. Chem. Soc.* **67**, 2079 (1945).

Fanta, P. E., Pandya, L. J., Groskopf, W. R., and Su, H.-J., *J. Org. Chem.* **28**, 413 (1963).

Freifelder, M., Smart, W. D., and Stone, G. R., *J. Org. Chem.* **27**, 2209 (1962).

Gilsdorf, R. T., and Nord, F. F., *J. Am. Chem. Soc.* **74**, 1837 (1952).

Hartung, W. H., *J. Am. Chem. Soc.* **50**, 3370 (1928).

Hartung, W. H., *J. Am. Chem. Soc.* **53**, 2248 (1931).

Hartung, W. H., and Chang, Y.-T., *J. Am. Chem. Soc.* **74**, 5927 (1952).

Hartung, W. H., and Munch, J. C., *J. Am. Chem. Soc.* **51**, 2262 (1929).

Hartung, W. H., Munch, J. C., Deckert, W. A., and Crossley, F., *J. Am. Chem. Soc.* **52**, 3317 (1930).

Hartung, W. H., Munch, J. C., Miller, E., and Crossley, F., *J. Am. Chem. Soc.* **53**, 4149 (1931).

Hartung, W. H., Munch, J. C., and Crossley, F. S., *J. Am. Chem. Soc.* **57**, 1091 (1935).

Hoy, K. L., and Hartung, W. H., *J. Org. Chem.* **23**, 967 (1958).

Hückel, W., and Kupka, R., *Chem. Ber.* **89**, 1694 (1956).

Hückel, W., and Thomas, K. D., *Ann. Chem. Liebigs* **645**, 177 (1961).

Islip, P. J., and White, A. C., *J. Chem. Soc.* p. 1201 (1964).

Jones, L. W., and Major, R. T., *J. Am. Chem. Soc.* **52**, 669 (1930).

Julian, P. L., Dailey, E. E., Printy, H. C., Cohen, H. L., and Hamashige, S., *J. Am. Chem. Soc.* **78**, 3503 (1956).

Karpenko, I., Unpublished observations, Engelhard Ind., 1958.

Koo, J., *J. Am. Chem. Soc.* **75**, 723 (1953).

Levin, N., Graham, B. E., and Kolloff, H. G., *J. Org. Chem.* **9**, 380 (1944).

Masamune, T., Ohno, M., Koshi, M., Ohuchi, S., and Iwardare, T., *J. Org. Chem.* **29**, 1419 (1964).

Matsumato, T., and Hata, K., *J. Am. Chem. Soc.* **79**, 5506 (1957).

Meltzer, R. I., and Lewis, A. D., *J. Org. Chem.* **22**, 612 (1957).

Mousseron, M., Froger, P., Granger, R., and Winternitz, F., *Bull. Soc. Chim. France* p. 843 (1947).

Müller, E., Fries, D., and Metzger, H., *Chem. Ber.* **88**, 1891 (1955).

Murphy, J. G., *J. Org. Chem.* **26**, 3104 (1961).

Neelakantan, L., and Hartung, W. H., *J. Org. Chem.* **23**, 964 (1958).

Ochiai, E., and Miyamoto, Y., *Yakugaku Zasshi* **57**, 583 (1937).

Paal, C., and Gerum, J., *Chem. Ber.* **42**, 1553 (1908).

Pfau, A. S., and Plattner, P. A., *Helv. Chim. Acta* **23**, 768 (1940).

Rebstock, M. C., *J. Am. Chem. Soc.* **73**, 3671 (1951).

Reeve, W., and Christian, J., *J. Am. Chem. Soc.* **78**, 860 (1956).

Reichert, B., and Koch, W., *Arch. Pharm.* **273**, 265 (1935).

Remers, W. A., Roth, R. H., and Weiss, M. J., *J. Org. Chem.* **30**, 2910 (1965).

Rosen, W. E., and Green, M. J., *J. Org. Chem.* **28**, 2797 (1963).

Rosenmund, K. W., and Pfannkuch, E., *Chem. Ber.* **56B**, 2258 (1923).

Rosenmund, K. W., Karg, E., and Marcus, F. K., *Chem. Ber.* **75B**, 1859 (1942).

Roth, W., Pigman, W., and Danishefsky, I., *Tetrahedron* **20**, 1675 (1964).

Rylander, P. N., and Steele, D. R., *Engelhard Ind. Tech. Bull.* **4**, 20 (1963).

Rylander, P. N., and Steele, D. R., *Engelhard Ind. Tech. Bull.* **5**, 113 (1965).

Smidt, J., Hafner, W., Jira, R., Sedlmeier, J., Sieber, R., Rüttinger, R., and Kojer, H., *Angew. Chem.* **71**, 176 (1959).

Turner, R. A., Huebner, C. F., and Scholz, C. R., *J. Am. Chem. Soc.* **71**, 2801 (1949).

Vanon, G., and Krajcinovic, M., *Bull. Soc. Chim. France* **43**, 231 (1928).

Vaughan, W. R., and Yoshimine, M., *J. Org. Chem.* **22**, 7 (1957).

Weijlard, J., Pfister, K., III, Swanezy, E. F., Robinson, C. A., and Tishler, M., *J. Am. Chem. Soc.* **73**, 1216 (1951).

Wenkert, E., Bernstein, B. S., and Udelhofen, J. H., *J. Am. Chem. Soc.* **80**, 4899 (1958).

Wilbert, G., and Sosis, P., U.S. Patent 3,028,429, Apr. 3, 1962.

10

Nitroso Compounds

Nitroso compounds with an α-hydrogen atom readily rearrange to the corresponding oxime (Taylor and Baker, 1945). Either the nitroso or oximino form may undergo hydrogenation, and it has been proposed that another tautomer, the unsaturated hydroxylamine, may also participate in the reduction (Rosen and Green, 1963):

$$-\overset{\underset{\displaystyle |}{H}}{\underset{\underset{\displaystyle H}{\displaystyle |}}{C}}-\overset{\underset{\displaystyle |}{H}}{C}-NO \rightleftharpoons -\overset{\underset{\displaystyle |}{H}}{C}-\overset{\underset{\displaystyle |}{H}}{C}=NOH \rightleftharpoons -C=\overset{\underset{\displaystyle |}{H}}{C}-NHOH$$
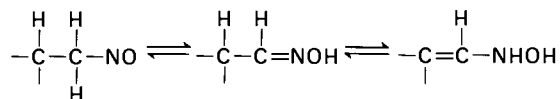
For convenience, most compounds capable of rearrangement to an oximino form are discussed in Chapter 9. The present discussion of the nitroso function is limited primarily to compounds that have no hydrogen atom adjacent to the nitroso function. A short discussion of the hydrogenation of nitric oxide to hydroxylamine is also included.

I. HYDROXYLAMINE

Hydroxylamine may be formed by hydrogenation of nitric oxide over platinum metal catalysts:

$$2NO + 3H_2 \longrightarrow 2NH_2OH$$
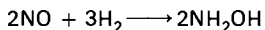
The reduction is carried out in acidic media and at temperatures that vary with the catalyst. A temperature range of 65–80°C has been taught as the preferred range (Belgian Patent 634,876). Another patent teaches 0–10°C as the preferred range (Benson, 1953), and another 30–85°C when a platinum–silver-on-carbon catalyst is used (Belgian Patent 654,171). The yield of hydroxylamine depends upon the pH of the medium and the nitric oxide to hydrogen ratios (Benson et al., 1956). A moderately acidic medium is necessary to prevent further reaction of the hydroxylamine. At pH values lower

than 2.5, hydroxylamine is not reduced by hydrogen at room temperature in the presence of platinum catalysts even at 1100 psig but is converted by nitric oxide to other products. Probably for this reason the best results are obtained with an excess of hydrogen. Aqueous sulfuric, phosphoric, and hydrochloric acids were found to be suitable solvents. Platinum was the most effective catalyst, palladium less so, and iridium and ruthenium failed to give hydroxylamine. Optimum conditions allowed yields of 67–73% at 73–77% conversion of nitric oxide. Detailed procedures for carrying out this reduction have been given by Benson *et al.* (1956).

Considerable effort has been expended in providing a catalyst for use in synthesis of hydroxylamine that would have adequate commercial life under the necessarily corrosive reaction conditions, and the problem has been satisfactorily solved (Keith, 1963). Platinum catalysts containing 1–10% silver, gold, iridium, or palladium are said to be preferable to platinum alone (Wintersberger *et al.*, 1961). When supported on a graphite carrier these catalysts are said to be very resistant to corrosion. Platinum catalysts said to have high activity and long life for hydroxylamine production have been prepared by a two-stage reduction of platinic salts (Jockers and Meier, 1960). The merits of palladium catalysts have been extolled in another patent (Benson, 1953).

II. *N*-NITROSOAMINES

Catalytic hydrogenation of *N*-nitrosoamines may afford substituted hydrazines. Early attempts to prepare *N*, *N*-disubstituted hydrazines by catalytic hydrogenation of nitrosoamines were not encouraging (Paal and Yao, 1930), but the impetus provided by demand for hydrazines in the rocket and missile industry led to the development of quite satisfactory commercial procedures. The main problem was to achieve the reaction,

$$\begin{array}{ccc} R & & R \\ | & & | \\ N{-}NO + 2H_2 \longrightarrow & N{-}NH_2 + H_2O \\ | & & | \\ R & & R \end{array}$$
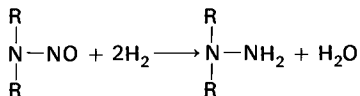
with minimum hydrogenolysis to the dialkylamine:

$$2R_2NNO + 3H_2 \longrightarrow 2H_2O + N_2 + 2R_2NH$$
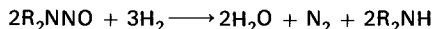
The products of reduction have been shown to depend on the type and amount of catalyst, temperature, pressure, and presence of various additives. In a study of the hydrogenation of *N*-nitrosodimethylamine over 10% palladium-on-carbon, the yield of product was found to be inversely related to the amount of catalyst used and fell to low values with large amounts of catalyst. The rate of reduction, which was zero order with respect to substrate,

was not proportional to the amount of catalyst, and apparently the reduction was badly hydrogen-deficient at high catalyst loadings. The effect of catalyst concentration on yield may therefore be also related to the agitation of the system, a factor not independently examined. Temperature had an important effect on yield, which fell almost linearly as the temperature was varied from 1°C to 63°C; at 1°C the yield was 83%, and at 63°C only 6%. The rate of reduction was almost independent of temperature in the range 25–63°C, and varied at low pressures approximately with the square of the pressure. The effect of pressure on yield was not stated. It was observed that the rate of reduction could be increased by frequent purging of the reactor. The rate was independent of the concentration of N-nitrosodimethylamine in the range 1–10%. At higher concentrations the rate of reduction fell as the reaction progressed, but the initial rate could be restored by purging the system (Klager, et al., 1960).

The major by-product in the reduction was dimethylamine, which apparently arose through decomposition of an intermediate tetramethyltetrazene (Paal and Yao, 1930). Tetramethyltetrazene was isolated from reduction mixtures and identified. No significant quantities of ammonia were found, which rules out direct hydrogenolysis of dimethylhydrazine as a major source of dimethylamine. Later workers showed that dimethylhydrazine was not reduced over 10% palladium-on-carbon under mild conditions, but that over rhodium-on-carbon hydrogenolysis did occur (Smith and Thatcher, 1962).

Diethylhydrazine can be formed in fair yields by hydrogenation of diethylnitrosoamine over palladium-, platinum-, and rhodium-on-carbon, but over Raney nickel the major product was diethylamine (Smith and Thatcher, 1962). When the reductions were carried out over the platinum metals, hydrogenations leading to the amine were suppressed by the presence of dissolved salts, and substantially improved yields of hydrazine were obtained. The improved results were not due to the specific nature of any one salt; ammonium acetate, lithium chloride, calcium chloride, magnesium sulfate, and tetramethylammonium bromide gave nearly the same results. The rate of reduction was also increased in the more polar media. These effects are general for a variety of nitrosoamines.

Palladium-on-carbon gave substantially higher yields of hydrazine than rhodium-on-carbon, but to obtain reasonable rates approximately 10 times as much palladium as rhodium was required. Best results were obtained at 25–30°C with rhodium catalysts, while 45–60°C was preferred with palladium. Higher temperatures favored hydrogenolysis.

The yield of hydrazine and, surprisingly, the rate of reduction were independent of the pressure between 50 and 1000 psig when palladium was the catalyst, but both yield and rate increased significantly with pressure when rhodium was used (Smith and Thatcher, 1962).

A patent issued to Feldman and Frampton (1964) teaches that catalyst deactivation in the reduction of *N*-nitrosodimethylamine over palladium-on-carbon is caused by contact of the catalyst with oxygen. A process is described in which the catalyst may be used and reused without contact with oxygen. Among the techniques mentioned for exclusion of oxygen is the use of deaerated water as a solvent. This patent also gives data relating the effect of temperature and catalyst concentration to the yield of dimethylhydrazine. Too high a temperature and too little catalyst both affect the yield and selectivity adversely. Excellent results were obtained at 26°C, 300 psig, and 0.07% (by weight) of 5% palladium-on-carbon.

Improved yields of hydrazines are obtained in the reduction of nitrosoamines over palladium, if ferrous or ferric ions are added to the reduction mixture. Only iron compounds gave improved results and then only if used with palladium. The optimum concentration of iron was about 0.5 mmole of iron per gm supported 5% palladium, but as little as 0.0005 mmole of iron had an appreciable effect (Tuemmler and Winkler, 1961). Further improvements were obtained by carrying out the hydrogenation in the presence of limited amounts of iron salts and alkali and alkaline earth hydroxides (Lima, 1964).

A continuous process has been described for vapor phase reduction of nitrosodimethylamine (Gaskins and Buyalos, 1964). The examples given are illustrated by use of a platinum-on-carbon catalyst. In one example, a 53% aqueous solution of nitrosodimethylamine, mixed with 85 moles of hydrogen, was vaporized and passed over 0.43% platinum-on-alumina at 100 psig and 88–95°C at a space velocity of 60 based on substrate. The yield of dimethylhydrazine was 80%. Another continuous process has been operated at 500–3000 psig and 30–75°C with a platinum or palladium-on-α-alumina or on periclase. Data are presented in the patent showing that the decrease in catalyst efficiency per unit time is directly related to the surface area. The best catalysts have low surface areas of the order of 6–10 square meters per gm (Moore and Pickens, 1965). Another continuous process used a two-phase system of water and toluene (Levering and Maury, 1958). In an example, a reactor was filled with 5% palladium-on-alumina (6–16 mesh), and then toluene and water were added in such amounts that the catalyst column was covered by toluene that floated on the water layer. The nitrosoamine was continuously introduced at the top of the reactor and hydrogen at 300 psig through a sparger at the bottom.

Apart from intensive effort to develop hydrogenation procedures for synthesis of hydrazines for use as rocket fuel, relatively little work has been done in this area. An attempt to prepare *N,N,N'*-trimethyltriazane by catalytic hydrogenation of nitrosotrimethylhydrazine failed. On reduction over 10% palladium-on-carbon in water, hydrogenolysis occurred and the product was trimethylhydrazine (Graefe, 1958).

$$(CH_3)_2NNNO \nrightarrow (CH_3)_2NNNH_2 + H_2O$$

with (CH_3)_2NNH—CH_3 branch, and CH_3 substituents on the N.
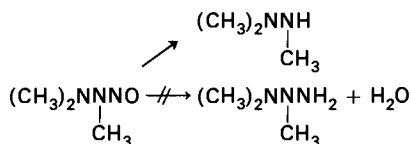
Some of the factors determining the yield of aminoguanidine from hydrogenation of nitro- and nitrosoguanidine have been examined:

$$H_2N-C(=NH)-NHNO_2 \longrightarrow H_2N-C(=NH)-NHNO \longrightarrow H_2N-C(=NH)-NHNH_2$$
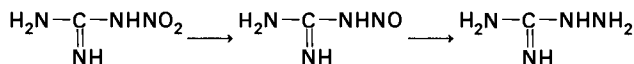
The sequence as written above does not occur in acidic media, and the yield of amine is always lower in acidic medium when starting from the nitroso compound. Over platinum oxide in acetic acid at 25°C, aminoguanidine is formed in 81.8% yield starting with nitroguanidine and in only 59.3% yield starting with nitrosoguanidine. The yields fall rapidly as the temperature is increased (Lieber and Smith, 1937).

Some unusual reactions of nitrosohydrazino compounds were recorded by Smith and Pars (1959). Hydrogenation of 5-(2-benzoyl-1-nitrosohydrazino)pentanoic acid (II), prepared by nitrosation of N-benzamidopiperidine (I), gave 1-benzamido-2-piperidone (III) and ammonia. The reduction was carried out over 5% palladium-on-carbon in ethanol.

(I) C₆H₅-C(=O)-NHN< (piperidine) →(HONO)→ (II) C₆H₅-CNHN(CH₂)₄COOH with =O and NO →(H₂)→ (III) C₆H₅-CNHN (with =O) benzamido-piperidone
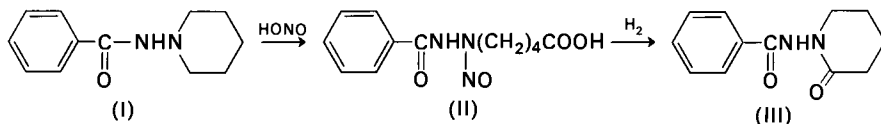
Nitrosation of N-benzamidopyrrolidine (IV) gave V, assumed to be in equilibrium with an open-chain aldehyde. Hydrogenation of V over 5% palladium-on-carbon in acetic acid gave IV.

(IV) C₆H₅-C(=O)-NHN< (pyrrolidine) ⇌ (HONO / H₂) (V) C₆H₅-C(=O)-N-N-NO with HO
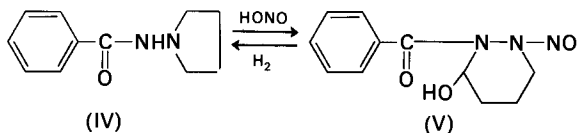
Aromatic nitroso compounds are reduced to the corresponding amines in 80–90% yield by refluxing with hydrazine in ethanol over 10% palladium-on-carbon. In the absence of a catalyst, partially reduced products are formed; nitrosobenzene is converted to azoxybenzene. With certain compounds Raney nickel gives better results than palladium (Pietra, 1957).

III. C-NITROSO COMPOUNDS

Aromatic nitroso compounds are readily reduced to the corresponding amine over palladium or platinum catalysts. For example, 0.1 mole of

p-nitrosothymol dissolved in 300 ml anhydrous ethanol was reduced quantitatively at atmospheric pressure to p-aminothymol over palladium-on-carbon (Sumerford *et al.*, 1940). Under more vigorous conditions (500 psig) an aqueous alkaline solution of p-nitrosodiphenylamine was reduced over palladium-on-carbon to the diamine. The nitroso compound may be reduced in its tautomeric form (Newby and Hunter, 1961).
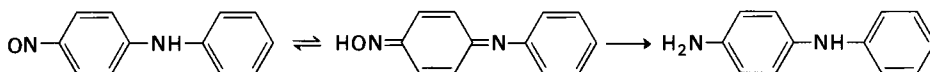
Examples of hydrogenation of nonaromatic nitroso compounds that cannot rearrange to an oxime are very few. Since the nitroso function in such compounds must be attached to a tertiary carbon atom, hydrogenation might be expected to be sluggish. For instance, hydrogenation of 9-nitroso-10-chlorodecalin (VI) to the amine (VIII) could not be carried out in a single step. The reduction was successful, however, when carried out in two steps with purification of the intermediate. Reduction of VI over prereduced platinum oxide in ethyl acetate afforded, after absorption of one equivalent of hydrogen, the 9-hydroxylamino compound (VII). This compound, after recrystallization from hexane, was further reduced to the amine over fresh prereduced platinum oxide in ethanol–dilute hydrochloric acid (Meinwald *et al.*, 1964).
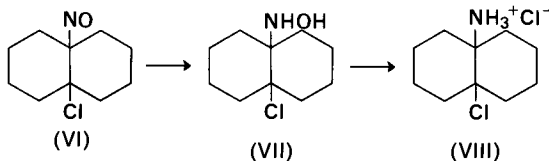
HYDROGENATION IN REACTIVE SOLVENTS

Hydrogenations of nitroso compounds may be carried out in solvents that interact with the amine or intermediate hydroxylamine as it is formed; acid anhydride solvents afford the acyl derivatives, formic acid the formyl derivatives, and aldehydic or ketonic solvents the alkyl derivatives. For example, hydrogenation over prereduced platinum oxide of 6-nitroso-4-cyclohexylresorcinol dissolved in acetic anhydride–acetic acid afforded (from chloroform) 6-acetylamino-4-cyclohexylresorcinol in 64% yield (McLamore, 1951). Similarly, reduction of 4-nitroso-5-isopropyl-2-methylphenol over platinum oxide in acetic anhydride–acetic acid afforded 4-acetoamido-5-isopropyl-2-methylphenol (Buchanan *et al.*, 1963).

Formyl derivatives were obtained by hydrogenation of nitrosopyrazoles in formic acid. Reduction of 2.0 gm 3-hydroxy-4-nitroso-5-aminopyrazole

(IX) in 40 ml 98 % formic acid over 10 % palladium-on-carbon afforded the diformyl derivative in 77 % yield, from which the free amine (X) could be obtained by hydrolysis (Taylor *et al.*, 1958).
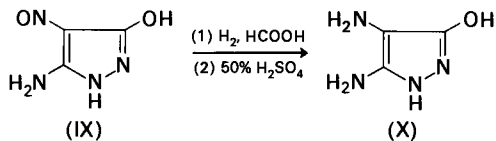
Nitrosation of an aromatic compound followed by hydrogenation in an aldehydic or ketonic solvent provides a convenient sequence for preparation of tertiary amines. Emerson (1947) has described the formation of tertiary amines by reduction of aromatic nitroso compounds over platinum oxide in the presence of aldehydes. Substituted phenylenediamines may be made by a similar sequence. For instance, reduction of 13.6 gm XI dissolved in 43 gm methyl ethyl ketone over 1 gm 5 % platinum-on-carbon at 750 psig and 100–160°C gave 15.6 gm XII (Jones and Fulton, 1955).
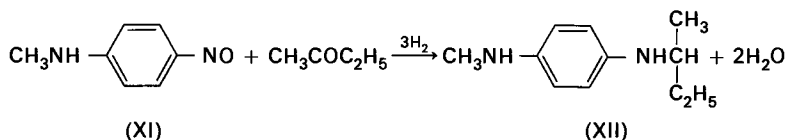
REFERENCES

Benson, R. E., U.S. Patent 2,628,888, Feb. 17, 1953.

Benson, R. E., Cairns, T. L., and Whitman, G. M., *J. Am. Chem. Soc.* **78**, 4202 (1956).

Buchanan, G. L., Raphael, R. A., and Still, I. W. J., *J. Chem. Soc.* p. 4372 (1963).

Emerson, W. S., U.S. Patent 2,414,031, Jan. 7, 1947.

Feldman, J., and Frampton, O. D., U.S. Patent 3,129,263, Apr. 14, 1964.

Gaskins, E., and Buyalos, E. J., U.S. Patent 3,133,120, May 12, 1964.

Graefe, A. F., *J. Org. Chem.* **23**, 1230 (1958).

Jockers, K., and Meier, H., German Patent 1,088,037, Sept. 1, 1960.

Jones, D. G., and Fulton, G. R., British Patent 728,509, Apr. 20, 1955.

Keith, C. D., Unpublished observations, Engelhard Ind., 1963.

Klager, K., Wilson, E. M., and Helmkamp, G. K., *Ind. Eng. Chem.* **52**, 119 (1960).

Levering, D. R., and Maury, L. G., British Patent 797,483, July 2, 1958.

Lieber, E., and Smith, G. B. L., *J. Am. Chem. Soc.* **59**, 1834 (1937).

Lima, D. A., U.S. Patent 3,154,538, Oct. 27, 1964.

McLamore, W. M., *J. Am. Chem. Soc.* **73**, 2225 (1951).

Meinwald, J., Meinwald, Y. C., and Baker, T. N., III, *J. Am. Chem. Soc.* **86**, 4074 (1964).

Moore, W. P., Jr., and Pickens, D., U.S. Patent 3,169,993, Feb. 16, 1965.

Newby, T. H., and Hunter, B. A., U.S. Patent 2,974,169, Mar. 7, 1961.

Paal, C., and Yao, W.-N., *Chem. Ber.* **63B**, 57 (1930).

Pietra, S., *Ann. Chim. (Rome)* **47**, 410 (1957).

Rosen, W. E., and Green, M. J., *J. Org. Chem.* **28**, 2797 (1963).

Smith, G. W., and Thatcher, D. N., *Ind. Eng. Chem. Prod. Res. Develop.* **1**, 117 (1962).

Smith, P. A. S., and Pars, H. G., *J. Org. Chem.* **24**, 1325 (1959).

Sumerford, W. T., Hartung, W. H., and Jenkins, G. L., *J. Am. Chem. Soc.* **62**, 2082 (1940).

Taylor, E. C., Barton, J. W., and Osdene, T. S., *J. Am. Chem. Soc.* **80**, 421 (1958).

Taylor, T. W. J., and Baker, W., "Sidgwick's Organic Chemistry of Nitrogen," p. 169. Oxford Univ. Press (Clarendon), London and New York, 1945.

Tuemmler, W. B., and Winkler, H. J. S., U.S. Patent 2,979,505, Apr. 11, 1961.

Wintersberger, K., Jockers, K., and Meier, H., U.S. Patent 3,009,779, Nov. 21, 1961.

11

Nitro Compounds

Aromatic nitro groups are easily hydrogenated to the corresponding aromatic amine. Palladium or platinum catalysts are by far the most used in these reductions; rhodium and ruthenium catalysts have as yet found only limited and specialized use. The reductions occur readily under mild conditions and usually without complication.

The aliphatic nitro group, on the other hand, is not so easily reduced. The rate of reduction is lower than for the aromatic nitro group and, furthermore, products of reduction may poison the catalyst (Yao and Emmett, 1961a). For these reasons successful reductions of aliphatic nitro groups are generally carried out with higher catalyst loading levels than would be necessary in reduction of aromatic compounds. In Table I the rates of hydrogenation of nitrobenzene and nitropropane in methanol over 5% palladium-, platinum-, rhodium-, and ruthenium-on-carbon are compared. Nitrobenzene is reduced 8–30 times more rapidly than nitropropane. The contrast is even greater in acetic acid solvent where all the catalysts in reduction of nitropropane, but not nitrobenzene, were quickly poisoned. (Karpenko, 1960).

TABLE I

HYDROGENATION OF NITROBENZENE AND NITROPROPANE IN METHANOL[a]

Catalyst (150 mg)	Nitropropane (ml H_2/minute)	Nitrobenzene (ml H_2/minute)
5% Pd/C	3	70
5% Pt/C	5[b]	40
5% Rh/C	0.3	10
5% Ru/C	0	0

[a] Atmospheric pressure, room temperature.
[b] Initial rate only, the rate constantly declined.

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I. CATALYSTS

—Excellent results have been obtained in hydrogenation of both aliphatic and aromatic nitro compounds over palladium, platinum, and rhodium. The catalyst of choice for any particular reduction will depend largely on other functional groups present and on the products required. Ruthenium does not seem to have an especial advantage, unless it is desired to saturate the ring as well in a single step (Whitman, 1952) or to obtain intermediate products. A detailed study of the hydrogenation of various aromatic nitro compounds over ruthenium dioxide has been made (Taya, 1962). The rate of hydrogenation in aqueous dioxane increased as the water content of the solvent was increased, in accord with other observations on the beneficial effect of water in ruthenium-catalyzed reduction (Rylander et al., 1963).

A thorough study has been made of platinum oxide catalysts in reduction of nitro compounds. Platinum oxide itself was shown to be catalytically inactive for hydrogenation of nitro compounds; hydrogenation takes place only over the reduced metal surface. Nitro compounds inhibit reduction of the catalyst to an active form, and aromatic nitro compounds are stronger inhibitors than aliphatic. The inhibition is greatest in neutral or alkaline medium (Yao and Emmett, 1961b), which may account for the poisoning effect of sodium hydroxide in reduction of nitrobenzene over platinum oxide (Adams et al., 1927).

Colloidal rhodium and palladium catalysts have been used to reduce a series of p-substituted nitrobenzenes to the amine. The surprising conclusion was reached that the reduction rates were affected by the electron-shifting properties of the substituents and by the presence of acid or base when the catalyst was rhodium, but over palladium neither of these factors affected the rates (Hernandez and Nord, 1947, 1948). This proposition was carefully reexamined, and it was found that substituents of nitrobenzene can affect the reaction rate over either palladium or rhodium only when the reaction is first order or fractional order with respect to the nitro compound. In essence the reduction under these conditions is diffusion-controlled and, because palladium is a more active catalyst, diffusion control occurs more easily over palladium, making it appear that the rates of reduction are independent of substituents or environment (Yao and Emmett, 1959).

II. SOLVENTS

Many solvents have been used with good results in hydrogenations of nitro compounds. In an early study of the reduction of nitrobenzene over platinum oxide (Adams et al., 1927), methanol, ethanol, propanol, acetone, and ethyl acetate were found to be excellent solvents while, surprisingly, acetic acid gave poor results. Many other workers have obtained excellent

results with acetic acid, however. Glycerol, glycol, water, and isopropanol were used as solvents for reduction of nitronaphthalene; their efficiency increased in the order given (Parrett and Lowy, 1926).

Hydrogenations of nitro compounds are usually carried out in acidic or neutral media. In some reductions the presence of acid has proved essential. Oelschläger (1956) hydrogenated a series of *m*-nitroacylbenzenes to *m*-alkyl-anilines, using a palladium sponge in the presence of sulfuric acid–acetic acid; in the absence of sulfuric acid not even traces of anilines were formed. (Particularly high yields were obtained in acid by dropwise addition of the substrate.) The presence of acids was necessary to achieve a good quality aminophenol by hydrogenation of nitrophenols over palladium- or platinum-on-carbon. Good results were obtained with dilute hydrochloric, sulfuric, or acetic acid; without acid the product was of low quality (Freifelder and Robinson, 1963). An acidic solvent proved necessary for preparation of optically active amines by reduction of optically active 2-nitrooctane over platinum oxide. In ethanol the resulting amine was 96% racemized due to racemization of unchanged substrate by free amine (Kornblum and Fishbein, 1955). On the other hand, the conclusion has been reached from kinetic studies that acid solutions have no decisive advantage over basic or neutral solutions in reduction of nitro compounds over colloidal palladium, rhodium, or platinum catalysts (Yao and Emmett, 1961b). Acid has at times, in fact, proved detrimental; as little as 1% acetic acid had a marked inhibiting effect on reduction of nitroparaffins over platinum oxide in 95% ethanol (Iffland and Cassis, 1952).

Some solvents may prove unsatisfactory because of interaction with other functions in the molecule. For instance, reduction of a series of *p*-nitro-benzoic acid esters in ethanol gave products boiling lower than expected. The difficulty was traced to an ester interchange and, when the reduction was carried out in benzene, rather than ethanol, the expected products were obtained in good yield (Kaye and Roberts, 1951). (Other examples of inter-action of solvent and substrate are given in the sections on condensation and rearrangement.)

The use of solvents in hydrogenation provides certain advantages, but they are not always essential. For instance, α-aminonaphthalene was obtained in 94% yield by reduction of molten α-nitronaphthalene over palladium oxide (Parrett and Lowy, 1926). A 98% yield of diaminotoluene was obtained by hydrogenation of molten dinitrotoluene over palladium-on-carbon (British Patent 832,153).

III. REDUCTION OF THE AROMATIC NITRO GROUP TO THE AMINE

The aromatic nitro function is easily reduced to the corresponding amine and the yields are usually very high. For instance, reduction of 1,8-dinitro-

naphthalene in ethanol over 30% palladium-on-carbon gave the diamine in 89–94% yield. Palladium was evidently slightly superior to platinum; when this reduction was carried out over platinum oxide, the product was blue-gray instead of white (Klemm et al., 1957). Hydrogenations of this compound over nickel catalysts were uniformly unsuccessful. A 92% yield of 3,5-diaminoanisole was obtained by reduction of the dinitro compound in warm ethanol over palladium-on-carbon (Garreau, 1946). Diaminotoluene has been formed in very high yield by hydrogenation over palladium-on-carbon with a water solvent (Benner and Stevenson, 1952), with alcohol–water solvent (Gardner and French, 1960), and in the molten state without solvent (British Patent 832,153). A special technique was employed when using water as a solvent. The substrate was added in small portions and the hydrogenation of each portion was completed before the next was added (Benner and Stevenson, 1952). Selective reductions of dinitro compounds may be achieved if the reduction is interrupted. Hydrogenation of 2,4-dinitro-aniline in ethanol–hydrochloric acid over 5% platinum-on-carbon afforded 4-amino-2-nitroaniline in 70% yield (Brunner and Halasz, 1963). The reduction was carried out with 18.3 gm substrate, 200 ml 96% ethanol, 20 ml concentrated hydrochloric acid, and 1 gm 5% platinum-on-carbon at 60°C and 50 psig.

Quantitative yields of 2,4,6-triaminotoluene were obtained by reduction of the trinitro compound over palladium-on-barium sulfate, a catalyst that, in this reduction, was superior to palladium-on-carbon or palladium-on-silica gel or platinum oxide (Hein and Wagner, 1935). Ethyl p-aminobenzoate is obtained in 91–100% yield by hydrogenation of ethyl p-nitrobenzoate in ethanol over platinum oxide (Adams and Cohen, 1941).

The list of successful reductions could be greatly extended. Probably in those compounds devoid of other reducible or interacting functions the amine usually is formed quantitatively, and the yield of product is determined by losses occurring in the isolation procedure.

OTHER SOURCES OF HYDROGEN

Various reducing agents may be used as sources of hydrogen in reduction of the nitro function. Three of these, each requiring a catalyst, are mentioned briefly below.

Aromatic nitro compounds may be smoothly reduced to amines over 5% palladium-on-carbon with hydrazine hydrate in refluxing alcohol as a source of hydrogen. Nitro derivatives of the reactive hydrocarbons perylene and pyrene reduced very rapidly, but those of the less reactive hydrocarbons reduced more slowly. Reduction of nitrobenzene was relatively very slow (Dewar and Mole, 1956). These observations suggested that hydrazine

functions in a more complicated way than by merely providing hydrogen through its own catalytic decomposition. Hydrogenations by this technique are probably most useful when a selectivity problem exists. For instance, *m*-chloronitrobenzene was reduced without dehydrochlorination to *m*-chloroaniline in 100% yield (Kuhn, 1951).

Nitro groups may also be reduced to amines in high yield through a catalytic transfer reaction with a hydrogen donor. This type of reaction has been reviewed by Jackman (1960), who pointed out that, for the most part, transfer hydrogenation is at present merely an alternative to direct hydrogenation. Alternatively, the transfer may be viewed as a dehydrogenation with the nitro compound acting as a hydrogen acceptor. The transfer reaction is probably the most useful when used in this sense. Transfer reactions have the merit that no special hydrogenation equipment is needed. For instance, 36 gm dimethyl 4-nitrophthalate in 500 ml absolute ethanol and 45 ml cyclohexene were refluxed over 0.60 gm palladium black for 18 hours to afford dimethyl 4-aminophthalate in 94.5% yield (Clendinning and Rauscher, 1961). One might guess that a direct hydrogenation with this amount of catalyst would have taken about 15–30 minutes at atmospheric pressure and room temperature.
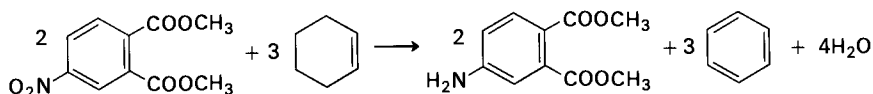
Aromatic nitro and nitroso compounds may be reduced to the amine in good yield by sodium borohydride in the presence of palladium-on-carbon. Without the catalyst, reduction normally does not occur. The reductions were carried out in alkaline solution or in aqueous methanol, and the rate of reduction was roughly proportional to the amount of catalyst used (Neilson *et al.*, 1962).

IV. REDUCTION OF ALIPHATIC NITRO GROUPS TO THE AMINE

Aliphatic nitro compounds, in contrast to the aromatic, are not so easily reduced. Many successful reductions of aliphatic nitro compounds are characterized by the use of high catalyst loadings, vigorous conditions, or relatively lengthy reaction times.

A. REACTION CONDITIONS

The two following examples indicate the vigorous conditions that have been employed in successful reductions. α-Amino-ω-lactams are prepared in high

yield by reduction of the corresponding nitro compound. For example, 50 gm α-nitro-ε-caprolactam gave 40 gm of the aminolactam when reduced over 5 gm palladium-on-carbon in 250 ml 96% methanol at 80°C and 2250 psig (German Patent 1,163,839). Nitroguanidine was reduced to aminoguanidine in good yield by carrying out the reduction in acid solution over platinum oxide. In neutral media the hydrogenolysis products ammonia and guanidine predominated. Aminoguanidine was formed in 82% yield by hydrogenating 20.8 gm nitroguanidine in 125 ml 15% aqueous acetic acid over 1 gm platinum oxide at 1875 psig and room temperature. The reduction was continued until hydrogen absorption ceased, at slightly more than three equivalents (Lieber and Smith, 1936).

$$\underset{\underset{NH}{\|}}{NH_2C}-NHNO_2 + 3H_2 \longrightarrow \underset{\underset{NH}{\|}}{NH_2C}-NHNH_2 + 2H_2O$$
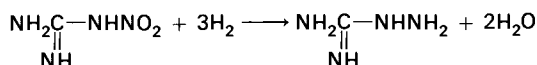
B. Catalyst Loading

Successful reductions of aliphatic nitro groups sometimes require high catalyst loading levels. The two following rather similar reductions were carried out with very different percentages of platinum oxide based on substrate. One reduction was successful with a 2% catalyst loading level, the other required 100%. Even the 2% loading level is, on a metal basis, much higher than is needed in hydrogenation of many aromatic nitro compounds.

Base-catalyzed condensation of a sugar with nitromethane followed by reduction and deamination provides a method for extending the carbon chain. D-Ribose was condensed with nitromethane in methanol containing sodium methoxide. The mixed sodio- aci-nitro alditols (52 gm) were dissolved in 25% aqueous acetic acid and reduced over platinum oxide (1 gm) at 25–45 psig (Barker, 1964).

$$
\begin{array}{ccc}
\begin{array}{l}
HC{=}O \\
HCOH \\
HCOH \\
HCOH \\
CH_2OH
\end{array}
&
\xrightarrow[\text{(2) } H_2]{\text{(1) } CH_3NO_2}
&
\begin{array}{l}
H_2CNH_2 \\
HCOH \\
HCOH \\
HCOH \\
HCOH \\
CH_2OH
\end{array}
\quad + \quad
\begin{array}{l}
H_2CNH_2 \\
HOCH \\
HCOH \\
HCOH \\
HCOH \\
CH_2OH
\end{array}
\end{array}
$$
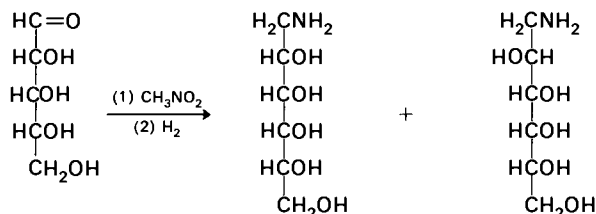
Successful reduction of the nitroglycoside, methyl 3-nitro-3-deoxy-α-hexopyranoside, to the corresponding amine required an amount of platinum oxide equal to the weight of the substrate. The nitroglycoside (5 gm) in dilute hydrochloric acid was reduced over 5 gm prereduced platinum oxide in 4.3 hours. Even at this high catalyst loading vigorous shaking was essential

or the hydrogenation rate became extremely slow, the catalyst being presumably deactivated by products of the reduction (Baer and Fischer, 1960).

C. REDUCTION TIME

The time required for hydrogenation of an aliphatic nitro group is apt to be quite long. For instance, Iffland and Cassis (1952) have described a convenient hydrogenation procedure for nitroparaffins. Freshly distilled nitroparaffin (0.2 mole) was dissolved in 100 ml 95% ethanol and shaken with 0.1 gm platinum oxide under 30–45 psig hydrogen pressure for 9 hours. The yields of primary amine from nitromethane, nitroethane, 1-nitropropane, 2-nitropropane, and 1-nitrobutane were, respectively, 48, 79, 83, 88, and 91%. Small amounts of hydrochloric acid in the hydrogenation solvent did not affect the yield or reduction time, but as little as 1% (by volume) of acetic acid in the solvent increased the time required for reduction by as much as 140–150% without, however, changing the yield. Larger amounts of acetic acid caused further increases in reduction time.

Acetic acid has been used with success as a solvent for a highly stereospecific hydrogenation over platinum oxide of dinitrocyclohexanes to the diamines. The reductions were carried out, however, on a millimole scale (Nielsen, 1962). Four equivalents were absorbed in about 1 hour followed by a slower addition of two more equivalents in 2 additional hours. The author suggested that this behavior implied the formation of a bis-hydroxylamine intermediate. Some reductions ceased altogether at this stage, but could be driven to completion by addition of more catalyst.

A step in the synthesis of the antibiotic chloromycetin involved hydrogenation of the aliphatic nitro function in 1-phenyl-2-nitro-1,3-propanediol to the amine. Reduction of 125 gm of the substrate in acetic acid over 3 gm palladium oxide required 23 hours for absorption of 3.15 equivalents of hydrogen. The yield of corresponding amine was good; evidently competitive hydrogenolysis of the benzylic hydroxyl function was kept to tolerable levels despite the extended reaction time (Controulis et $al.$, 1949).

$$\text{C}_6\text{H}_5\text{—CHOH—CH—CH}_2\text{OH} + 3\text{H}_2 \longrightarrow \text{C}_6\text{H}_5\text{—CHOHCHNH}_2\text{CH}_2\text{OH}$$
$$\underset{\text{NO}_2}{|}$$
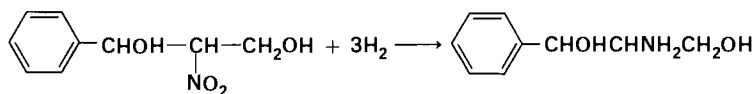
Prolonged hydrogenation (72 hours) of the nitro compound (I) over 30% palladium-on-carbon in acetic acid resulted in selective reduction of the aromatic ring rather than the nitro function. This work is especially interesting in that it illustrates how a small change in structure can produce totally different and unexpected results. Reduction of the very similar compound (II) occurred more in accordance with expectations, and provided a mixture

of 1-(α-carbethoxy-β-indolyl)-2-aminopropane and the corresponding lac-
tam. The unusual course followed in reduction of I was attributed to the
sterically crowded environment around the nitro function, which hindered
contact between the function and the catalyst surface (Young and Snyder,
1961).

(I) R = C$_2$H$_5$
(II) R = CH$_3$

R = C$_2$H$_5$
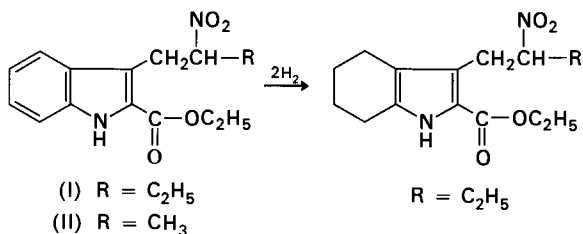
V. DIFUNCTIONAL COMPOUNDS

Since the nitro function itself can usually be reduced to the amine without
undue difficulty, most problems connected with its hydrogenation center
around the products of partial reduction and on the fate of other functional
groups in the molecule. The reduction of various difunctional molecules
will be considered first.

A. NITROOLEFINS WITH NONADJACENT FUNCTIONS

Complete reduction of nitroolefins in this group will give the corresponding
saturated amine. The problems connected with hydrogenation of these com-
pounds center primarily around selective reduction of one or the other
function. The outcome seems to depend largely on whether the nitro function
is aliphatic or aromatic. Inasmuch as the aliphatic nitro group is reduced
with more difficulty than the aromatic, one might expect selective reduction
of the olefinic function to occur more readily in compounds having an
aliphatic nitro group. Aliphatic nitroolefins may, in fact, usually be reduced
selectively to the corresponding nitroparaffin. A single example will suffice
here (other examples are given in Chapter 5 on hydrogenation of olefins).
endo-5-Nitronorbornene was selectively reduced over platinum oxide in
acetic acid to endo-2-nitronorbornane. Hydrogen absorption practically
ceased after absorption of one equivalent (Roberts et al., 1954).
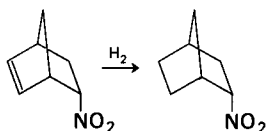
When the competition is between an aromatic nitro function and an olefin, selective reduction of the nitro group is more probable. For instance, in hydrogenation of α-(1-naphthyl)-o-nitrocinnamic acid over platinum oxide in absolute ethanol, the nitro function was preferentially reduced and the unsaturated amine was formed in 76% yield (Fieser and Joshel, 1940).
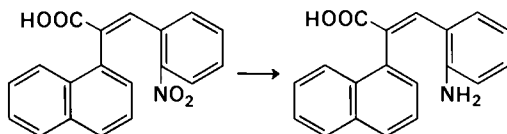
Another example is provided by the selective reduction of 2-chloro-methyl-2-(p-nitrostyryl)-1,3-dioxolane to the corresponding unsaturated amine over platinum oxide in ethyl acetate. The nitro group was reduced in 15 minutes, the olefin required 48 hours (Baker and Jordaan, 1965).
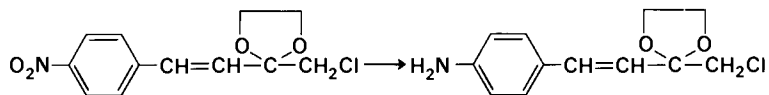
Reduction of m-nitrobenzalacetophenone and m-nitrobenzalacetone over platinum oxide in ethanol stopped spontaneously at the aminoolefin stage, but if the solvent contained a small amount of acetic acid the olefin was reduced as well (Adams et al., 1927).
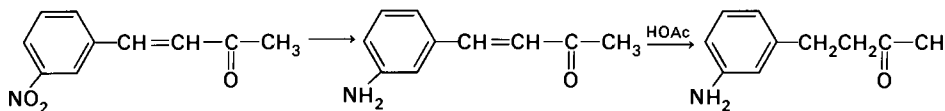
B. CONJUGATED NITROOLEFINS

Hydrogenation of conjugated nitroolefins presents a number of problems. Various intermediate reduction products may be formed as well as dimers. The conclusion has been reached that the behavior of α,β-unsaturated nitro compounds on catalytic reduction is essentially the same as that of α,β-unsaturated ketones (Kohler and Drake, 1923). The resulting saturated nitro compounds, however, undergo further reduction; the successive formal steps were postulated to be:

$$RCH=CHNO_2 \longrightarrow RCH_2CH_2NO_2 \longrightarrow [RCH_2CH_2NO] \longrightarrow RCH_2CH=NOH \longrightarrow$$

$$RCH_2CH=NH \longrightarrow RCH_2CH_2NH_2$$
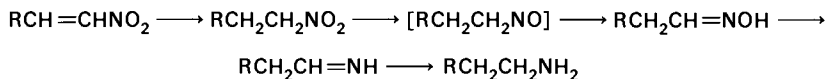
1. Dimers

Dimerization occurs readily in neutral media. The major product from reduction of β-nitrostyrene over platinum black in ethanol was, after

absorption of one equivalent of hydrogen, α,δ-dinitro-β,γ-diphenylbutane. In acetic acid the reduction proceeded more rapidly, and phenylacetaldehyde oxime was formed along with the dimer (Sonn and Schellenberg, 1917).
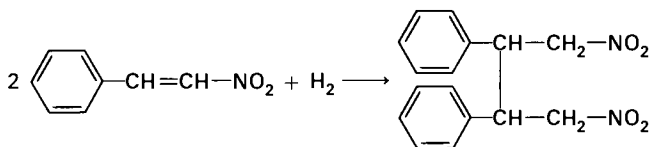
In an extension of this work, to include reduction of nitrostilbene, β,β-diphenylnitroethylene, and β,β-diphenyldinitroethylene, it was found that formation of dimolecular products could be largely prevented by carrying out the reduction in the presence of mineral acids (Kohler and Drake, 1923). Reduction of nitrostyrene in ethanol or ether over platinum black gave mainly dimolecular products, but reduction in methanol containing dry hydrogen chloride gave dimers in only 4% yield.

2. Oximes

Oximes may be obtained in excellent yield by hydrogenation of α,β-unsaturated nitro compounds. Reduction of β-nitrostyrenes in pyridine over palladium-on-carbon gave almost quantitative yields of the oximes of substituted phenylacetaldehydes (Reichert and Koch, 1935). Similarly, hydrogenation of 2,4-bis(β-nitrovinyl)anisole gave the dioxime in 85% yield (Reichert and Marquardt, 1950). When the method was applied to hydrogenation of 1-nitrocyclooctene and 1-nitro-1-octadecene, the yields of oximes were only about 60%. These relatively low yields were attributed to loss of substrate through addition of piperidine (formed in the reaction) to the nitroolefin (Seifert and Condit, 1963).
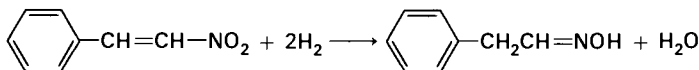
Oximes may be formed in good yield by hydrogenation of nitroolefins in acidic media. Hydrogenation over palladium-on-carbon of 1-nitrocyclooctene in methanol containing 0.5–1.0 equivalent of hydrogen chloride gave the oxime in 83% yield accompanied by 17% cyclooctanone. A similar hydrogenation of 1-nitro-1-octadecene gave stearaldoxime in 73% yield and 13% of a carbonyl compound, assumed to be stearaldehyde. The authors suggest that the carbonyl compound arises in these reductions by 1,4-addition of hydrogen to the substrate and subsequent Nef decomposition of the resulting aci-form of the nitroparaffin to nitrous oxide and the carbonyl compound (Seifert and Condit, 1963).

Formation of an oxime by reduction of an unsaturated nitro compound provided important evidence for proof of structure of 4-nitro-2,3-dihydro-benzo[b]thiepin 1,1-dioxide. This compound, formed by direct nitration, was reduced over 10% palladium-on-carbon or platinum dioxide in dioxane. Hydrogenation stopped after absorption of two equivalents of hydrogen to given an oxime, providing thereby direct evidence that the nitro group had entered the heterocyclic ring (Love, 1964).
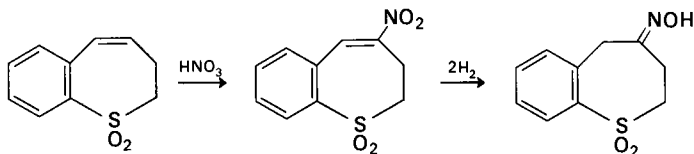
3. Saturated Amines

Formation of saturated amines by hydrogenation of conjugated nitro-olefins seems to be best accomplished by use of an acetic acid–mineral acid solvent. The effectiveness of mineral acid in these systems is strikingly illustrated by a report on the hydrogenation of β-nitrostyrene. In sulfuric acid–acetic acid, the hydrogenation was complete in 8 minutes and gave a 90% yield of β-phenylethylamine; in the absence of sulfuric acid, the reduction required about 10 hours and the yield of amine was very low (Kindler et al., 1934). The sulfuric acid–acetic acid solvent system has been used with advantage in hydrogenation of trisubstituted β-nitrostyrenes over palladium black (Dyumaev and Belostotskaya, 1962). Acetic acid–hydrochloric acid was used for reduction of 2-methoxy-4,5-methylenedioxy-β-nitrostyrene over 5% palladium-on-carbon (Daly et al., 1961). The use of 7–8% palladium-on-barium sulfate has been taught as the preferred catalyst for hydrogenation of 2,5-dimethoxy-β-nitrostyrene in acetic acid–sulfuric acid. After extraction and distillation the phenylethylamine was obtained in 70% yield (Green, 1962).
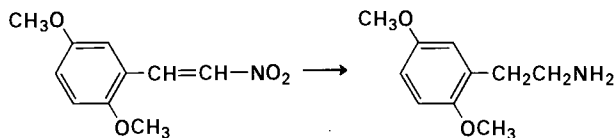
4. Unsaturated Amines

Preferential hydrogenation of the nitro function in conjugated nitro-olefins seems to be contingent upon some special structural feature of the substrate that makes the olefinic linkage relatively difficult to reduce. The tetrasubstituted enol double bond, a structure usually difficult to reduce,

survived hydrogenation of 3-nitro-4-hydroxycoumarin in methanol–hydro-chloric acid over palladium-on-carbon (Huebner and Link, 1945):
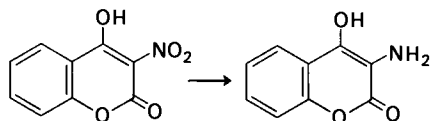
Similarly, formation of the aminouracil (IV) by hydrogenation of III probably depends in part on the resistance of the tetrasubstituted double bond to reduction (Papesch, 1962).
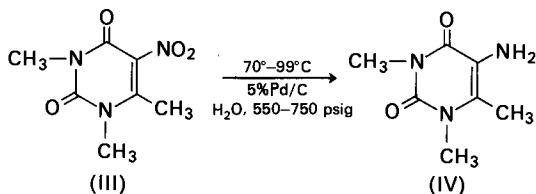
The nitro function of nitromarmesin was selectively reduced over platinum oxide in acetic acid. The lactonic double bond remained unaffected even though no effort was made to limit hydrogen absorption. The double bond in this compound does not seem so inaccessible or so stable as to have permitted prediction of this reduction product (Abu-Mustafa and Fayez, 1961).
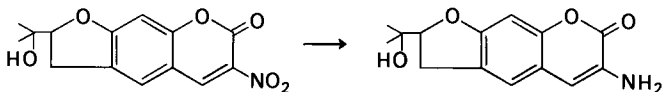
C. Nitro Nitriles

Aromatic nitro compounds containing a nitrile group, situated so as to preclude intramolecular interaction, may be selectively reduced to the amino nitrile without difficulty. For instance, a series of 2-(dialkylamino-alkoxy)-4-nitrobenzonitriles was readily reduced to the corresponding amino nitriles. The reductions were carried out over platinum oxide in 80% aqueous ethanol, and the rapid absorption ceased abruptly after three equivalents of hydrogen had been consumed (Clinton and Laskowski, 1952).
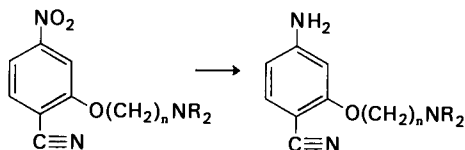
On the other hand, the reduction may follow a quite different course if the nitrile and nitro functions are not spatially isolated. Several examples of ring formation involving both functions have been given elsewhere (Section V, G on cyclizations). An interesting type of interaction between adjacent functions took place in hydrogenation of *o*-nitrobenzonitrile over either platinum or palladium catalysts in water or methanol solvent (Rupe and Vogler, 1925). The product was *o*-aminobenzamide, formed, as experiments in heavy water proved, by transfer of an oxygen atom from the nitro to the nitrile group (Moll *et al.*, 1963).
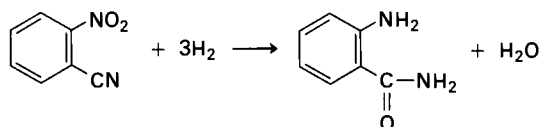
A single example will suffice to point out that the strong tendency toward preferential reduction of the nitro function that exists in aromatic compounds does not necessarily apply to aliphatic nitro compounds. Hydrogenation of 4-nitro-4-methylvaleronitrile over 5% palladium-on-carbon in acetic acid proceeded with preferential reduction of the nitrile, and 4-nitro-4-methylpentylamine was isolated in 64% yield (Young, 1958). Preferential hydrogenation of the nitrile in this compound is no doubt facilitated by steric factors limiting approach of the catalyst to the nitro group.

D. NITRO KETONES

Aromatic nitro compounds containing a ketonic function may be selectively reduced to the amino ketone. For instance, Mannich bases derived from *p*-nitroacetophenone are selectively reduced to the amino ketones over 5% palladium-on-carbon in methanol (Wheatley *et al.*, 1954). Reduction of 6-nitro-3-methoxyphenacylglycine over palladium black in sulfuric acid gives the corresponding amine in 81% yield (Makino and Takahashi, 1954).
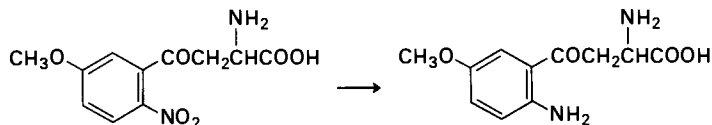
A more impressive example of selectivity is found in the hydrogenation of V over platinum oxide in 95% ethanol. Three equivalents of hydrogen were rapidly absorbed to reduce the nitro function, followed by a slower absorption of an additional three equivalents to form the piperidine (VI) (Truitt *et al.*, 1952) (other aspects of selectivity in hydrogenation of phenacylpyridinium salts are discussed in this reference).

$$O_2N-\!\!\langle\ \rangle\!\!-COCH_2-\overset{+}{N}\!\langle\ \rangle\!-C_6H_{13} \;\longrightarrow\; H_2N-\!\!\langle\ \rangle\!\!-COCH_2-\overset{+}{N}\!\langle\ \rangle\!-C_6H_{13}$$
$$\qquad\qquad\qquad\quad Br^-\qquad\qquad\qquad\qquad\qquad\qquad Br^-$$
$$\qquad\qquad\qquad\quad (V)\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad (VI)$$
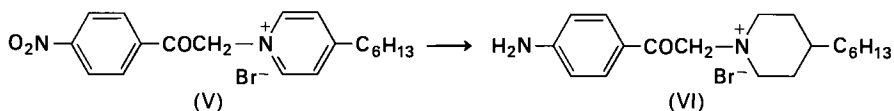
The nitro function in aromatic nitro ketones tends to be selectively reduced, probably because the nitro function is adsorbed preferentially on the catalyst. Acetophenone is reduced over 5% ruthenium-on-carbon at a fair rate; nitrobenzene is reduced very slowly. Nonetheless in hydrogenation of *m*-nitroacetophenone over ruthenium-on-carbon the nitro group is reduced preferentially and at a very slow rate (Karpenko, 1960).

E. NITRO OXIMES

The nitro function in nitro oximes may be reduced preferentially. When the nitro group is aromatic, selective reduction to the amino oxime should be particularly straightforward. For instance, a series of *o*-amino oximes, for use as intermediates in preparation of quinazolines, was prepared by reducing the nitro oxime over 5% palladium-on-carbon in ethanol. The yields were 70–90% (Armarego, 1962).
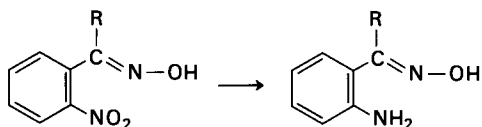
For purposes of classification, nitrolic acids may be viewed as nitro oximes. Reduction of these compounds may afford amidines. Adipomononitrolic acid was reduced in water containing ammonia to monoadipamidine over Raney nickel or 5% platinum-on-carbon at 1400 psig and temperatures below 20°C (Lonchamp and Baumgartner, 1963).

$$NH_2(CH_2)_5\underset{NO_2}{C}=NOH \;\longrightarrow\; NH_2(CH_2)_5\underset{NH}{\overset{\|}{C}}-NH_2$$
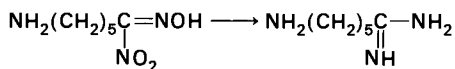
F. HALOGEN-CONTAINING NITRO COMPOUNDS

Hydrogenation without dehydrohalogenation of a nitro compound containing aromatic halogen sometimes presents a formidable problem. The problem is particularly difficult when the halogen is activated, as for example in the halonitrobenzenes. In this case the derived amino function is also an activator, unless cationic (Baltzly and Phillips, 1946). The ease of concomitant or subsequent dehydrohalogenation depends among other

things on the halogen (increasing generally) in the order, fluorine < chlorine < bromine < iodine), on the amount of catalyst, on the solvent, on the activity of the catalyst (Kindler *et al.*, 1953), on the catalytic metal, and on the support. By appropriate choice of catalyst and conditions, dehydrohalogenation may usually be kept to low levels.

Of the halogens, fluorine is the most resistant to dehydrohalogenation and aromatic fluoronitro compounds can be reduced to the corresponding fluoroamines without difficulty. Good yields of the fluoroamine have been obtained with palladium black or Raney nickel catalysts (Vorozhtsov *et al.*, 1961), and several such compounds were reduced with a 5% palladium-on-carbon catalyst in methanol without a trace of dehydrohalogenation (Karpenko, 1960).

1. Catalysts

Reduction of aromatic chloro or bromo nitrocompounds without dehydrohalogenation is sometimes difficult. The extent of dehydrohalogenation depends on the metal, the type of catalyst, and the support. Table II compares the extent of dehydrohalogenation during reduction of *p*-chloronitrobenzene in ethanol over palladium, platinum, and rhodium on various supports (Rylander *et al.*, 1965). Palladium catalysts had evidently best be avoided if the haloaniline is the desired product. On the other hand, if the halogen-free amine is desired, palladium is the catalyst of choice, for it is

TABLE II

HYDROGENATION OF *p*-CHLORONITROBENZENE: EFFECT OF CATALYST SUPPORT AND METAL[a]

	Palladium		Platinum		Rhodium	
Support	Dehydrohalo-genation (%)	Time (sec)	Dehydrohalo-genation (%)	Time (sec)	Dehydrohalo-genation (%)	Time (sec)
Carbon	53	340	23	550	2	2070
Calcium carbonate	34	745	21	570	—	—
Strontium carbonate	—	—	14	1200	1	3900
Barium carbonate	26	780	6	1260	1	300
Alumina	48	490	22	770	4	4800
Barium sulfate	35	510	21	1500	—	—
Kieselguhr	50	385	15	1360	—	—
Magnesium silicate	35	445	—	—	—	—

[a] All catalysts contained 5% by weight of metal. Hydrogenations were conducted at atmospheric pressure and room temperature with 200 mg catalyst, 1.5 gm substrate, and 50 ml ethanol. Each reduction was stopped at three equivalents of hydrogen absorbed in the time noted and the free halogen formed at this point determined by titration.

also the best of the platinum metals for dehydrohalogenation of haloanilines. Platinum and rhodium give relatively little dehydrohalogenation and are indicated when loss of halogen is to be minimized. Platinum has usually been used for reduction of halonitroaromatics but, generalizing from the limited results published so far, rhodium may prove as useful.

The percentage of dehydrohalogenation depends also on the amount of catalyst, decreasing as the amount of catalyst is decreased (Table III). This same trend was observed in other work involving competitive dehydrohalogenation and hydrogenation (Freifelder et al., 1961).

TABLE III

HYDROGENATION OF p-CHLORONITROBENZENE: EFFECT OF AMOUNT OF CATALYST[a]

5% Pd/C (mg)	Dehydrohalogenation (%)
50	40.0
100	45.0
200	53.0
300	54.0

[a] Hydrogenations were conducted at atmospheric pressure and room temperature with 1.5 gm substrate and 50 ml ethanol. Each reduction was stopped at three equivalents of hydrogen absorbed and the free halogen formed at this point determined by titration.

Reduction of halonitroaromatics without dehydrohalogenation may be readily accomplished by employing an unusual type of catalyst, sulfided platinum metals (Belgian Patent 643,911).* There was no detectable dehydrochlorination of chloronitrobenzenes when they were reduced over the sulfides of palladium, platinum, rhodium, or ruthenium. In hydrogenation of bromonitrobenzenes there was no debromination over platinum sulfide, trace debromination with rhodium sulfide, and appreciable debromination with palladium sulfide. These catalysts are also applicable to selective reduction of polyhalonitroaromatics. For instance, a mixture of 103.5 gm 2,5-dichloronitrobenzene, 230 ml methanol, and 3.0 gm 5% platinum sulfide-on-carbon was reduced at 85°C and 500–800 psig for 1.25 hours. At this point hydrogen absorption stopped and 2,5-dichloroaniline was obtained in 99.5% yield (Dovell and Greenfield, 1965).

2. Solvent

The solvent may have a decisive influence on the outcome of a reduction of nitrohaloaromatics. For instance, hydrogenation of 4-nitro-2-chlorobenzoic acid or its ethyl ester over 5% palladium-on-barium sulfate in

* Manufactured by Engelhard Industries, Newark, N.J.

ethyl acetate gave quantitative yields of 4-amino-2-chlorobenzoic acid or its ethyl ester, respectively. When the reduction was carried out in isopropanol, four equivalents were absorbed at constant rate and 4-aminobenzoic acid or the ethyl ester was isolated in 90% and 100% yields (Weizmann, 1949).

$$R = H, C_2H_5$$
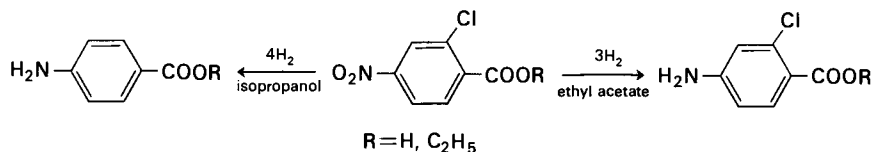
3. Inhibitors

The extent of dehydrohalogenation may also be influenced by the purity of the substrate. Reduction of a 1-bromo-3-nitronaphthalene, which had not contacted hypophosphoric acid in its preparation, proceeded over either platinum oxide or 10% palladium-on-carbon in ethanol to afford 1-bromo-3-naphthylamine in 60–75 yield. However, when hypophosphoric acid was used in preparation of the substrate, no reduction occurred unless the material was first distilled *in vacuo*. The yield of bromonaphthylamine from hydrogenation of the distilled substrate was quantitative (Bergmann and Blum, 1961). One might surmise that the distilled material still contained a catalyst deactivator but in diminished quantity so that the reduction could proceed.
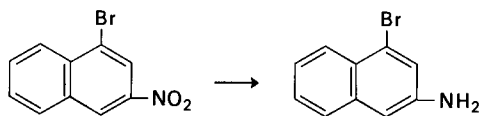
Bases of various kinds are frequently used to promote dehydrohalogenation but, paradoxically, bases have been used to good advantage in inhibiting loss of halogen during reduction of halonitrobenzenes. For instance, platinum-on-carbon in the presence of regulated amounts of magnesium oxide or hydroxide has been claimed as a preferred system for reduction of the nitro function with minimum loss of halogen. The magnesium compound should be present in amounts of 0.1–1.0% by weight, based on substrate; less does not inhibit dehydrohalogenation and more promotes it (Spiegler, 1963). Similarly, rhodium in the presence of calcium hydroxide has been used for this same purpose. When calcium hydroxide is present, reductions proceed at an accelerated rate and catalyst life is much longer (Dietzler and Keil, 1962). Palladium-on-carbon in the presence of sodium acetate has been used for reduction of 3-chloronitrobenzenes to chloroanilines in high yield. The reduction is carried out without solvent. No appreciable hydrogenolysis of the halogen occurs. In an example, 4500 gm 3-chloronitrobenzene, 200 gm sodium acetate, and 4.5 gm 5% palladium-on-carbon were charged to a

stirred reactor. After 4 hours at 80°C and 75 psig, 3460 gm 3-chloroaniline was recovered by distillation (German Patent 1,159,956).

4. Pyridines

The strong tendency of palladium to cause dehydrohalogenation in nitro-halobenzenes also applies to pyridine derivatives. Reduction of 6-chloro-5-nitro-2-picoline over platinum oxide–palladium-on-barium carbonate in ethyl acetate containing a small amount of ethanol gave 5-amino-2-picoline. The halogen could be retained if the reduction were carried out over platinum oxide (Parker and Shive, 1947). Similarly, the halogen was largely retained and the nitrile unchanged when VII was reduced over platinum oxide in ethanol (Bruce and Perez-Medina, 1947).

$$
\begin{array}{ccc}
& Cl & \\
O_2N & & CN \\
& & \\
CH_3 & N & Cl \\
& (VII) &
\end{array}
\longrightarrow
\begin{array}{ccc}
& Cl & \\
H_2N & & CN \\
& & \\
CH_3 & N & Cl \\
& (50\%) &
\end{array}
$$
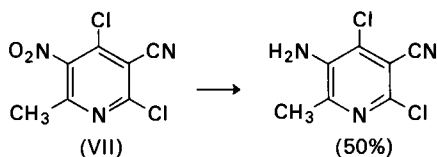
A key step in a synthesis of 6-chloropyridoxine involved the reaction,

$$
\begin{array}{ccc}
& COOCH_3 & \\
O_2N & & C\equiv N \\
& & \\
CH_3 & N & Cl \\
& (VIII) &
\end{array}
\longrightarrow
\begin{array}{ccc}
& COOH & \\
H_2N & & COOH \\
& & \\
CH_3 & N & Cl \\
& (IX) &
\end{array}
$$
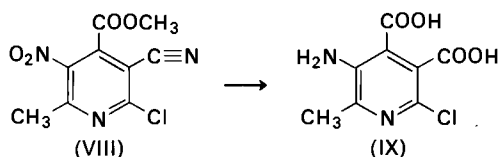
which called for catalytic hydrogenation of the nitro group and simultaneous hydrolysis of the ester and nitrile functions, but without simultaneous loss of the labile chlorine by hydrolysis or hydrogenolysis. When VIII was reduced over platinum oxide in 20% hydrochloric acid, three moles of hydrogen were rapidly taken up and then the reaction essentially stopped to afford IX in high yield. The yield was lower when palladium-on-carbon was used instead of platinum oxide, or when the ethyl ester was used instead of the methyl (Blackwood et al., 1958). Other examples of the reduction of chloronitropyridines, involving retention of chlorine over platinum and loss of chlorine over palladium, have been published by Harris and Folkers (1939) and Harris et al. (1939).

5. Other Products

Reduction of halonitro compounds need not necessarily lead to the corresponding amines. Hydrogenation of p-nitrochlorobenzene over 5% palladium-on-carbon in acetic acid at 75°C and 1850 psig gave N-cyclohexylaniline in 74% yield. The same product was obtained in a similar

hydrogenation of the *ortho* isomer (Luvisi, 1964). Platinum does not appear, from the examples cited in the reference, to be as effective as palladium in this reduction.

$$2 \quad \text{(o-chloronitrobenzene)} \longrightarrow \text{(phenyl)-}\overset{H}{\underset{}{N}}\text{-(cyclohexyl)}$$
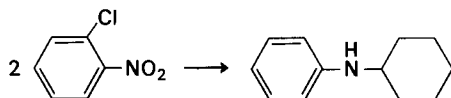
Hydrogenation of 1-chloro-1-nitrocyclohexane gave several products depending on the conditions. Reduction in methanol over 10% palladium-on-carbon gave cyclohexanone oxime in 80% yield; over platinum oxide in ethanol, *N*-cyclohexylhydroxylamine was formed in 65% yield (Robertson, 1948). Reduction over palladium-on-carbon in aqueous alkali gave nitro-cyclohexane.

$$\text{(cyclohexyl)}=\text{NOH} \xleftarrow[\text{CH}_3\text{OH}]{\text{Pd/C}} \text{(1-chloro-1-nitrocyclohexane)} \xrightarrow[\text{C}_2\text{H}_2\text{OH}]{\text{PtO}_2} \text{(cyclohexyl)-NHOH}$$

$$\downarrow{\substack{\text{Pd/C} \\ \text{OH}^-}}$$

$$\text{(cyclohexyl)-NO}_2$$
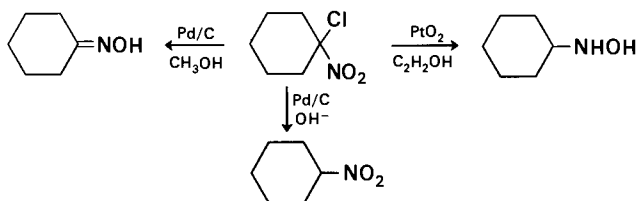
G. CYCLIZATIONS

Products of nitro group reduction, i.e., amines, oximes, and hydroxyl-amines, may interact with other functional groups and with each other. Interaction is particularly likely to occur when their spatial arrangements are such as to favor formation of rings. The strong tendency toward ring formation frequently forces involvement of functional groups that otherwise would have emerged from the hydrogenation unchanged. These cyclizations offer convenient routes to a variety of nitrogen heterocyclic compounds, some of which are obtained by other means only with difficulty. Below, selected examples illustrate the interaction of the nitro function with various functional groups during catalytic hydrogenation.

1. *Nitro Carboxylic Acids*

Reduction of a nitro function in a molecule containing a suitably disposed carboxyl function can easily lead to a lactam. Hydrogenation of 2-(*o*-nitrophenyl)-1,2,5,6-tetrahydrobenzoic acid proceeded smoothly over plati-num oxide in ethyl acetate to give the saturated lactam, plus a small amount of amino acid (Masamune *et al.*, 1964). Whether a lactam or an amino acid results in reduction of nitro acids depends on the severity of the conditions

and the length of time that the reaction is continued after hydrogen absorption ceases (Walker, 1955).
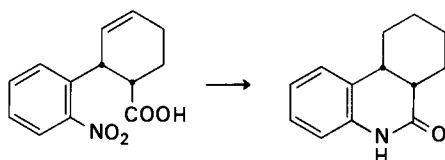
Quinoxalines may be formed by reduction of an appropriate nitroaniline followed by treatment of the intermediate cyclization product with alkaline hydrogen peroxide (Munk and Schultz, 1952).
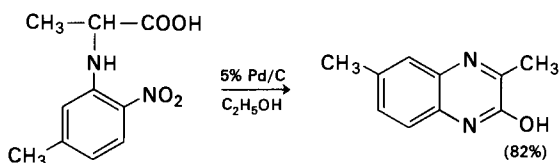
If cyclization occurs before the nitro group is reduced to the amine, other products may arise. For instance, catalytic hydrogenation of o-nitrophenylalanine (free base) in ethanol over platinum oxide yields o-aminophenylalanine, which readily cyclizes in acidic medium to form 3-amino-3,4-dihydrocarbostyril (Davis et al., 1963). However, the same hydrogenation procedure using the hydrochloride salt of o-nitrophenylalanine gave 3-amino-3,4-dihydro-1-hydroxycarbostyril hydrochloride. Apparently the reaction proceeds through formation of an intermediate hydroxylamino compound from partial hydrogenation of the nitro group, followed by cyclization (Davis et al., 1964).
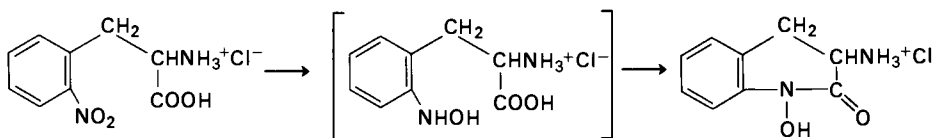
2. Nitro Amides

The products obtained on hydrogenation of X over platinum oxide depended on the solvent; cyclization to the N-oxide was favored, as in the previous example, by acid. Reduction of X in 50% aqueous ethanol, 95% ethanol, absolute ethanol, or ethyl acetate gave good yields of XI in all cases. However, if one equivalent or more of hydrochloric acid were present during the reduction, the hydrochloride of the N-oxide (XII) was obtained in good yield. Evidently acid catalyzes cyclization of an intermediate hydroxylamine

to a point where ring closure is faster than reduction to the primary amine (Schulenberg and Archer, 1965)

The tendency of suitably situated *o*-amino amides toward cyclization permits use of the *o*-nitrophenoxyacetyl group as a protecting group in peptide synthesis. The nitro function is first reduced to the amine over platinum oxide in water containing sodium bicarbonate and then, after separation of the *o*-aminophenoxyacetyl peptide, the protecting group is removed by hydrolysis at 100°C. When the solution is cooled the lactam crystallizes, while the peptide remains in the aqueous solution and can be recovered in good yield (Holley and Holley, 1952).

3. Nitro Nitriles

Reductive cyclization of *o*-nitrophenylacetonitriles offers a route to indoles. The reduction proceeds through an intermediate amino nitrile. Hydrogenation of XIII over palladium-on-carbon at room temperature in ethyl acetate afforded the amino nitrile (XIV), but when the reduction was conducted at 80°C the indole (XV) was obtained in 60% yield. The indole was prepared by shaking 5.0 gm XIII in 150 ml ethyl acetate with 2.5 gm 10% palladium-on-carbon at 40 psig and 80°C for 1.5 hours. Three moles of hydrogen were absorbed in 12 minutes and an additional mole in 15 minutes more.

The first products of the reduction, the amino nitriles, undergo cyclization to an amidine. In acetic acid the reduction stops at this stage. The author suggested that further reduction is prevented because of resonance stabilization of an amidinium salt, or because of inability of the catalyst to adsorb a protonated amidine. In ethyl acetate the reduction continues to an indole (Walker, 1955) (see, however, page 215).

Amine oxides may arise by condensation of a partially reduced nitro function with a nitrile. Catalytic reduction of o-nitrocinnamonitriles over palladium in ethanol proceeded with ring closure to yield the 2-amino-quinoline-N-oxides (Bauer, 1938).

$$R = C_6H_5, -COOC_2H_5$$
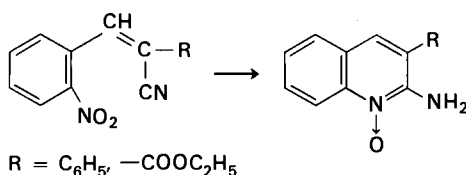
4. Nitro Esters

Ring closure between an amine and ester provided an intermediate in an easy route to pyrrolizidine. Reduction of dimethyl γ-nitropimelate over platinum oxide in methanol led to the lactam. Further reduction over copper chromite at 250°C and 5000–6000 psig gave pyrrolizidine in 60% overall yield (Leonard et al., 1947). A similar sort of reduction and cyclization was used for preparation of pyrrolidines (Leonard and Beck, 1948).
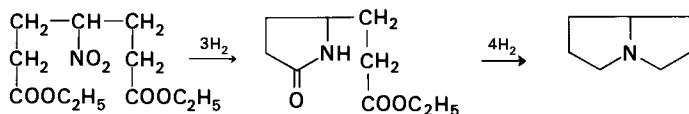
A route to the isoquinoline system involves condensation of o-phthalaldehyde and nitromethane, oxidation with potassium dichromate and sulfuric acid, and reduction of the resulting nitrolactone over platinum oxide in aqueous acetic acid. The isoquinoline probably arises through reduction of the nitro function, hydrogenolysis of the benzylic lactone, and cyclization. If the reduction is prolonged, seven equivalents are absorbed and octahydroisocarbostyril can be isolated in 57% yield (Baer and Achmatowicz, 1964a,b).
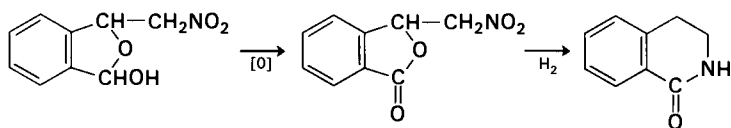
5. Dinitro Compounds

A general way into the indole system involves reductive cyclization of a dinitrostyrene (Huebner et al., 1953). The following example illustrates the cyclization as well as a remarkable migration of iodine (Heacock et al., 1963). The reduction was carried out in ethyl acetate–ethanol–acetic acid solvent over 10% palladium-on-carbon. The solvent derived from earlier work on a similar ring closure (Huebner et al., 1953). Acetic acid was present to remove the ammonia formed, and ethanol was present to prevent flocculation of the catalyst by ammonium acetate.
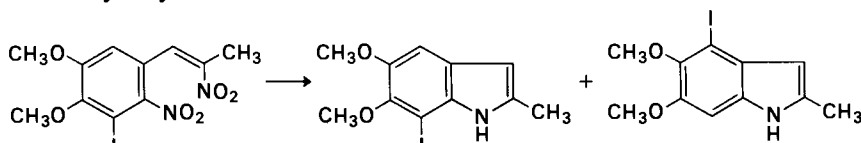
In reduction of a similar dinitrostyrene (XVI) to the indole (XVII), the solvent system methanol–acetic acid–ethyl acetate proved decidedly disadvantageous. When XVI was hydrogenated over 10% palladium-on-carbon the absorption stopped at 60% of the theoretical and no XVII could be isolated (Benington et al., 1960). The authors reasoned that in acidic media a stable, intermediate, protonated ion similar to the protonated amidinium ion postulated by Walker (1955) might be formed and, accordingly, repeated the reduction in ethyl acetate–methanol. In this system the hydrogenation was rapid and quantitative and XVII was isolated in 50% yield.
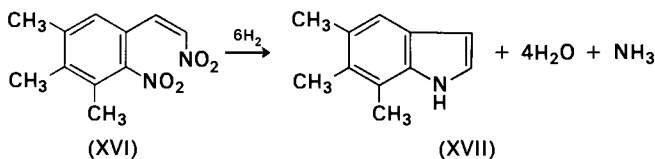
Cinnolines may be formed in catalytic hydrogenation of 2,2′-dinitro-biphenyls. For instance, reduction of 2,2′-dinitro-4,4′-bis(trifluoromethyl)-diphenyl (XVIII) in ethyl acetate over platinum oxide gave a mixture of the
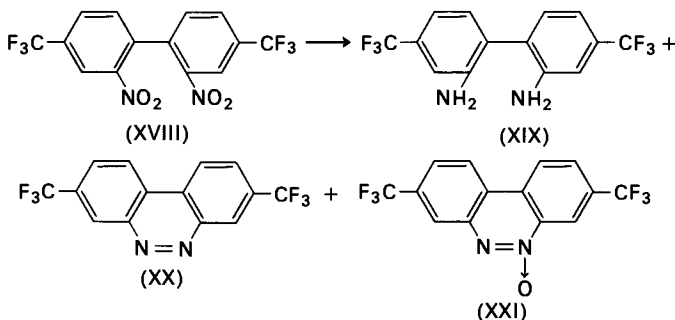
diamine (XIX), the benzo[*c*]cinnoline (XX), and the benzo[*c*]cinnoline oxide (XXI). The benzo[*c*]cinnoline (XX) is not an intermediate in the formation of the diamine, for under the conditions of the reaction it is not further reduced. The authors suggested that the diamine and the cinnolines arise from two different orientations of the dinitro compound adsorbed on the catalyst. When the nitro groups are *trans* to one another, formation of the diamine is likely since the *trans* configuration prevents interaction of either the nitro groups or their reduction products. Conversely, a *cis* orientation should favor interaction and cinnoline formation (Ross and Kuntz, 1952). Reduction of 2,2′-dinitrobiphenyl over platinum oxide in ethanol–ethyl acetate proceeded smoothly to the diamine without, apparently, benzo[*c*]cinnoline formation (Blood and Noller, 1957). Benzo[*c*]cinnoline is formed in reduction over Raney nickel but by proper choice of conditions its formation can be avoided.

6. Nitro Ketones

Hydrogenation of γ-nitro ketones may give pyrrolidines in good yields. Hydrogenation of the nitro ketone (XXII) over platinum oxide gave the corresponding pyrrolidine (XXIV) in 86% yield, but only a small amount of pyrrolidine was formed when XXIII was the substrate (Kohler and Drake, 1923). However, over Raney nickel in the presence of ammonia, XXIII afforded XXV in 82% yield (Kloetzel, 1947).

$$C_6H_5CHCH_2COR$$
$$\overset{|}{C}H_2NO_2$$

(XXII)   R = CH_3 (XXIV)   R = CH_3
(XXIII)   R = C_6H_5 (XXV)   R = C_6H_5
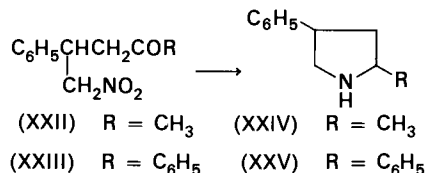
H. Condensations

Disubstituted diphenylamines are obtained when aromatic nitro compounds substituted in the *para* position are hydrogenated in the presence of reactive second components in hydrogen fluoride solvent. Nitro compounds substituted in the *para* position with halogens and amino or carboxy groups

X = $-OCH_3$, $-OC_2H_5$, $-CH_3$, $-C_2H_5$, $-C_6H_5$
Y = $-OH$, $-OCH_3$, $-NH_2$, $-NHC_6H_5$
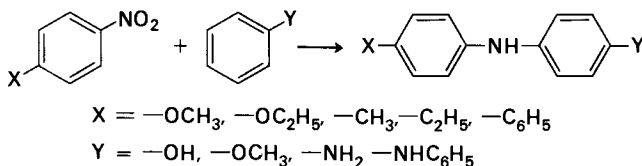
are reduced mainly to the normally expected amines, rather than undergoing condensation. Mixtures of diphenylamines and aminobiphenyls are obtained from nitro compounds not substituted in the *para* position.

A typical reductive condensation is illustrated by the synthesis of 4-hydroxy-4'-methoxydiphenylamine. A mixture of 115 gm *p*-nitroanisole, 94 gm phenol, 5 gm 3% palladium-on-carbon, and 120 gm anhydrous hydrogen fluoride was hydrogenated at 40–45°C and 195–300 psig. The yield of 4-hydroxy-4'-methoxydiphenylamine was 66% based on *p*-nitroanisole charged, or 100% based on *p*-nitroanisole consumed in the condensation (Weinmayr, 1955).

Polymers

Compounds containing functions that interact readily with amines may form polymers when the position of the functions is not conducive to ring formation. For instance, attempts to reduce in a single operation the carbonyl and nitro groups of 1-(*o*-nitrobenzyl)-2,3-dioxopyrrolidine over platinum oxide failed. Resinous products were obtained, due probably to condensation of the rapidly formed aromatic amino group with an unreduced keto carbonyl group in another molecule (Southwick and Casanova, 1958). Similarly, reduction of *m*- and *p*-nitrobenzaldehyde gave polymers of a Schiff's base type (Phillips and Maggiolo, 1950). Polymer formation sometimes occurs with unexpected ease, as in the reduction of *p*-nitrobenzyl alcohol over platinum oxide in methanol, which gave an 80% yield of an insoluble polymer; reduction of the *meta* isomer under the same conditions gave *m*-aminobenzyl alcohol in quantitative yield (Phillips and Maggiolo, 1950).

VI. REARRANGEMENTS

N-Phenylhydroxylamines undergo rearrangement in acidic media to *p*-substituted anilines. *N*-Phenylhydroxylamine is converted to *p*-fluoroaniline in hydrogen fluoride (Titov and Baryshnikova, 1953), to *p*-hydroxyaniline in sulfuric acid, and to *p*-chloroaniline in concentrated hydrochloric acid (Taylor and Baker, 1945). When the reduction of nitrobenzene is carried out in acidic media in such a way that *N*-phenylhydroxylamine is an intermediate, rearranged products can occur. The catalytic hydrogenation of nitrobenzene as a source of *p*-haloaniline and of *p*-hydroxyaniline has been examined in detail. The major problem connected with these syntheses involves limiting the competing reactions leading to aniline, which may arise by further reduction of *N*-phenylhydroxylamine or directly from nitrobenzene without formation of intermediate phenylhydroxylamine.

A. *p*-FLUOROANILINE

Platinum oxide was found to be the best catalyst for synthesis of *p*-fluoro-aniline by hydrogenation of nitrobenzene in anhydrous hydrogen fluoride (Fidler *et al.*, 1961). Palladium-on-carbon, palladium oxide, and platinum-on-carbon could also be used, but were not as effective as platinum oxide. *p*-Fluoroaniline could be obtained in 61 % yield, based on 100 % conversion of nitrobenzene, when the reduction was carried out at 55 psig and 50°C. The yield dropped to about 25 % when the temperature was raised (120°C) or lowered (13°C) or when the pressure was raised (500 psig).

In a typical reduction, 25 gm nitrobenzene, 0.25 gm platinum oxide, and 140 gm anhydrous hydrogen fluoride were charged to a monel autoclave and heated to 50°C. Hydrogen pressure was maintained at about 20 psig above the pressure of hydrogen fluoride until absorption ceased, usually in slight excess of two equivalents. Cooling was necessary to maintain the temperature at 50°C.

B. *p*-AMINOPHENOL

Under carefully controlled conditions *p*-aminophenols may be obtained in good yields by reduction of nitrobenzenes in dilute sulfuric acid over platinum catalysts (Spiegler, 1956):

$$\langle C_6H_5 \rangle\text{-}NO_2 + 2H_2 \longrightarrow HO\text{-}\langle C_6H_4 \rangle\text{-}NH_2 + H_2O$$
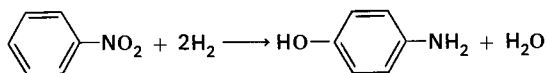
The yield is sensitive to acid concentration, catalyst, temperature, hydrogen pressure, mode of addition, and presence of water-soluble quaternary ammonium compounds. Satisfactory yields of *p*-aminophenols may be obtained only at reduced hydrogen pressure. In a test situation the yield of *p*-aminophenol approached 100 % at 100 mm hydrogen pressure, fell to 50 % at 500 mm, and was negligible at atmospheric pressure. Much better rates were obtained if the nitrobenzene were added gradually to the reaction vessel at such a rate that no appreciable amount of it remained undissolved in the reaction medium. This technique obviated the high speed stirrers required in earlier work. Improved rates and yields were obtained by carrying out the reduction in the presence of a small amount of a water-soluble quaternary ammonium compound. In a comparative test, small amounts (0.5–0.7 gm for about 2000 gm reaction mixture) of octadecyl-trimethylammonium chloride doubled the reduction rate and increased the yield of *p*-aminophenol from 55 % to 80 %. The effect produced by these compounds is said to be not merely a result of their dispersing action, since improvement is obtained with quaternary ammonium compounds that are

not dispersing agents and is not obtained with other dispersing agents that are not quaternaries. The rate of reduction increases steadily with temperature, but the yield of *p*-aminophenol increases to a maximum and then decreases. The temperature at which this maximum occurs depends on the hydrogen partial pressure. At 500–540 mm the yield is maximum at 115°C, at 240–300 mm at 100°C. The strength of the sulfuric acid solution required depends in part on the temperature. If the acid is too dilute incomplete rearrangement occurs, especially at lower operating temperatures, and if too concentrated side-reactions occur, especially at high operating temperatures. The acid should be present in a concentration of at least 10% by weight.

In a typical example, a 10-gallon glass-lined reaction kettle, equipped with a propeller agitator, was charged with 2250 gm 96% sulfuric acid, 20,500 gm copper-free water, 10.5 gm *C*-cetyl betaine, and 177 gm 1% platinum-on-carbon. The kettle was flushed with hydrogen and heated to 100°C. The partial pressure of hydrogen was maintained at 200 mm while nitrobenzene was added gradually in 25 gm portions. In this manner 2500 gm nitrobenzene was reduced in 5 hours to afford *p*-aminophenol in 83.2% yield and aniline in 16.8% yield.

C. ACETYL TRANSFER

Hydrogenation of *p*-nitrophenyl acetate over platinum oxide gave, through an acetyl transfer, *p*-hydroxyacetanilide rather than the desired *p*-aminophenyl acetate. The reduction was carried out at 850 psig and 120°C with 290 gm substrate, 500 ml absolute ethanol, and 2.5 gm platinum oxide. These are very vigorous conditions for this reduction, and failure to obtain *p*-aminophenyl acetate can probably best be attributed to the hydrogenation conditions rather than to some aspect of the catalytic process itself (Feldstein *et al.*, 1961).
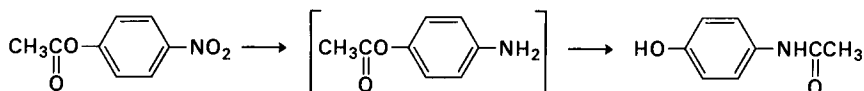
VII. LOSS OF NITROGEN BY HYDROGENOLYSIS

Loss of nitrogen from a molecule through hydrogenolysis of the nitro function or its reduction products is usually an unimportant reaction, but may occur readily in some compounds. For instance, reduction of the polynitro compounds, 2,2,3,3-tetranitrobutane and 3,3,4,4-tetranitrohexane,

over platinum oxide in ethanol gave the corresponding diamines in 70%
yield (Grabiel *et al.*, 1955):

$$R-CH_2-\overset{\displaystyle NO_2}{\underset{\displaystyle NO_2}{C}}-\overset{\displaystyle NO_2}{\underset{\displaystyle NO_2}{C}}-CH_2-R \longrightarrow R-CH_2\overset{}{\underset{\displaystyle NH_2}{CH}}-\overset{}{\underset{\displaystyle NH_2}{CH}}CH_2-R$$
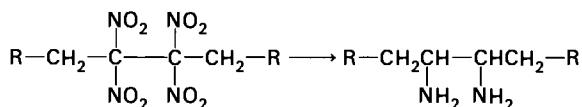
A more usual type of hydrogenolysis occurs by cleavage of the nitrogen–
nitrogen bond in nitroamines, Hafner and Evans (1957) reduced XXVI to
XXVII in 57% yield over palladium black in 15% acetic acid. The hydro-
genation was carried out at slightly above atmospheric pressure by stirring
a mixture of 0.469 gm XXVI with 0.06 gm palladium black in 15% acetic
acid solution for 20 hours.

(XXVI)   (XXVII)
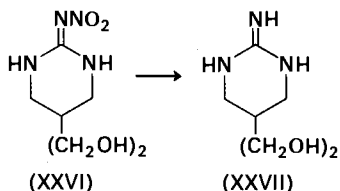
Reduction of nitroguanidine in neutral aqueous media at low pressure
over platinum oxide gives predominantly the hydrogenolysis products
ammonia and guanidine (Lieber and Smith, 1936) but, if the reduction is
interrupted after absorption of one equivalent of hydrogen, fair yields of
nitrosoguanidine may be obtained (Lieber and Smith, 1935).

VIII. PRODUCTS OF PARTIAL REDUCTION

Catalytic hydrogenation of nitro groups may give partially reduced
products containing nitroso, oxime, hydroxylamine, azo, and hydrazo
functions. These partially reduced compounds are sometimes sought and
sometimes appear as unwanted products of the reduction.

A. HYDROXYLAMINES

Hydroxylamines are sometimes obtained under conditions where complete
reduction to the amine would have been expected. The examples are too few
to disentangle how much of the hydroxylamine formation is attributable to
some intrinsic structural feature of the molecule, how much derives from
deactivation of the catalyst by the substrate, and how much is due to the
type of catalyst employed.

The hydroxylamine (XXIX) was obtained on hydrogenation of ethyl 2-methyl-5-nitronicotinate (XVIII) over platinum oxide in absolute ethanol even when the reduction was carried out at 900 psig. The hydroxylamine was obtained in 45% yield together with a 46% yield of the amine (XXX). By carrying out the reduction in acetic acid–acetic anhydride, only the amine was obtained as its acetyl derivative (Fanta, 1953).
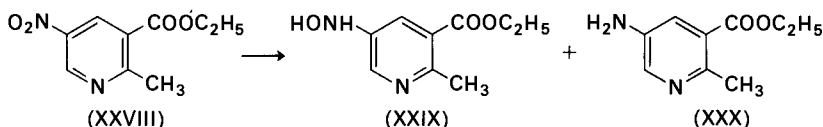
Attempts to reduce 2-p-nitrobenzenesulfonamido-3-ethoxypyridine to the corresponding amine in ethanol with a palladium hydroxide-on-calcium carbonate catalyst gave only 2-p-hydroxylaminobenzenesulfonamido-3-ethoxypyridine (Roblin and Winnek, 1940). The reduction was carried out with 3.2 gm substrate in 200 ml 95% ethanol over 1.0 gm palladium hydroxide-on-calcium carbonate at 50°C. Two 0.5 gm portions of fresh catalyst were added during the course of the reduction, but even so the hydroxylamine resulted.
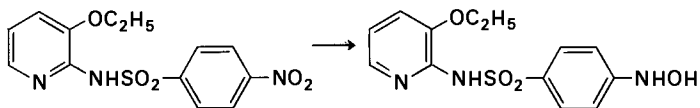
Hydrogenation of di(p-nitrocarbobenzoxy)-L-cystine over palladium-on-carbon gave L-cysteine and p-tolylhydroxylamine (Berse et al., 1957). Presumably the divalent sulfur deactivated the palladium catalyst sufficiently so that the hydroxylamine was not reduced further to toluidine. A complex aliphatic amino nitro compound, 3-nitro-3-(2-diethylaminoethylamino)-methyl-1,5-dioxaspiro[5.5]undecane was converted to the hydroxylamino derivative in 62% yield when reduced over 5% platinum-on-carbon in ethanol at 60 psig initial pressure. The reduction stopped spontaneously at this stage, perhaps because of partial deactivation of the platinum catalyst by the free amines. Compounds in this series were reduced readily to the amine over Raney nickel at elevated pressures (Schipper et al., 1961).

Hydrogenation of nitro compounds carried out in the presence of carbonyl compounds may give coupling products derived by interaction of the carbonyl and the intermediate hydroxylamine. Reduction of a mixture of nitrobenzene and benzaldehyde over platinum afforded first the nitrone and then the substituted hydroxylamine (Vavon and Krajcinovic, 1928).

$$C_6H_5NO_2 + C_6H_5CHO \longrightarrow C_6H_5\underset{\underset{O}{\downarrow}}{N} = CHC_6H_5 \longrightarrow C_6H_5\underset{\underset{OH}{|}}{N} - CH_2C_6H_5$$
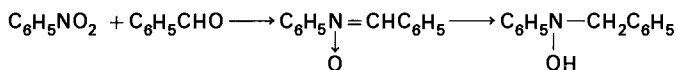
Hydroxylamines may be obtained by choice in good yield by proper selection of reaction conditions, by use of catalyst deactivators, or by limiting the available hydrogen. Reduction of 4-chloro-6-nitro-1,3-benzene-disulfonamide over 5% palladium-on-barium sulfate in ethanol containing oxalic acid gave the corresponding hydroxylamino compound, when the reduction was stopped after absorption of two moles (Goldkamp, 1964).
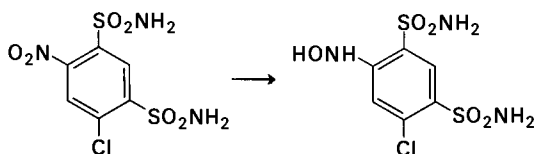
The use of oxalic acid in this reduction probably stemmed from the work of Schmidt et al. (1925), who obtained excellent yields of hydroxylamines and hydroxylamino alcohols as the oxalates by hydrogenation of aliphatic nitro alcohols and nitromethane over 5% palladium-on-barium sulfate. For instance, 9 gm methylhydroxylamine oxalate was obtained by hydrogenation of 6.1 gm nitromethane, 6.3 gm oxalic acid, and 1 gm catalyst in 77 ml water. N-Alkylhydroxylamines have also been obtained from hydrogenation of a nitroalkane over a platinum metal in the presence of at least one equivalent of sulfuric acid per mole of nitroalkane (Japanese Patent 14,655/64).

Methylhydroxylamine and cyclohexylhydroxylamine were prepared in 90% yield by hydrogenating the corresponding nitro compounds at room temperature and pressure over finely divided palladium (Kahr and Zimmermann, 1957). Cyclohexylhydroxylamine has also been prepared by hydrogenating nitrocyclohexane in 10 volumes of water containing one equivalent of acetic acid over 5% palladium-on-alumina at 15–75 psig (Joris and Vitrone, 1958). N-Methylhydroxylamine sulfate was prepared by reduction of nitromethane over palladium-on-carbon in a solvent immiscible with water and containing one equivalent of sulfuric acid. For example, 684 gm nitromethane and 684 gm toluene, 2 gm 5% palladium-on-carbon, and 1010 gm 60% sulfuric acid were hydrogenated at 600 psig and 50°C until absorption ceased. The product consisted of 92% N-methylhydroxylamine sulfate, 6% methylamine sulfate, and 2% unchanged nitromethane (McWhorter, 1965).

A synthesis of cyclohexanone oxime involves selective hydrogenation of nitrocyclohexane to cyclohexylhydroxylamine, followed by oxidation to the oxime. The reduction is carried out in methanol over a 1% palladium-on-calcium carbonate catalyst at 10–20°C and subatmospheric pressure (Meister and Franke, 1959). A similar process involves the use of platinum metal catalysts partially deactivated by addition of sulfur or nitrogen compounds to the mixture (Japanese Patent 18,126/64).

Cyclohexylhydroxylamine has also been prepared by hydrogenation of nitrocyclohexane in continuous processing. The hydroxylamine was obtained in 95% yield by passing downward 27 gm nitrocyclohexane and 0.7 gm cyclohexylamine dissolved in 250 ml cyclohexane over 50 gm 8-mesh 0.5% palladium-on-alumina. Hydrogen pressure was maintained at about 1 atm and the temperatures kept below 40°C (Joris, 1961).

B. OXIMES

Oximes are readily reduced to either hydroxylamines or amines. The formation of oximes by hydrogenation of saturated nitro compounds consequently requires the use of a catalyst relatively inactive for further reduction of the oxime. (Oximes derived from α,β-unsaturated nitro compounds are discussed in Section V on difunctional compounds.)

Palladium catalysts deactivated by lead have given good yields of oximes by hydrogenation of aliphatic nitro compounds. For instance, 258 gm nitrocyclohexane, 600 gm water, 2.58 gm 5% palladium-on-acetylene black, and 1.4 gm lead oxide gave a 79.2% yield of cyclohexanone oxime by hydrogenation at 160°C and 500 psig. Lead nitrate, sulfate, and carbonate may also be used (Foster and Kirby, 1961). When no lead was present the yield of oxime was only 11.6%. Magnesium-promoted palladium or platinum catalysts were also used in this synthesis.

Another catalyst for synthesis of cyclohexanone oxime was prepared from chloroplatinic acid, zinc nitrate, calcium nitrate, and ammonium chromate. Hydrogenation of 50 gm nitrocyclohexane in 50 ml methanol with 2 gm catalyst at 105°C and 1500 psig gave cyclohexanone oxime in 65% yield (Weise, 1954). Other catalysts for the reduction contain two metal components from an extensive list in addition to a platinum metal (Japanese Patent 14,226/64).

C. NITROSO

Nitroguanidine has been reduced to nitrosoguanidine over both platinum oxide and Raney nickel. The yields are 56–59% with platinum and 36–44% with nickel. Water, methanol, ethanol, dioxane, and benzene were used as reaction media; water was found to be the most suitable solvent for use with the platinum catalyst.

$$H_2N\underset{\underset{NH}{\|}}{C}-NHNO_2 \xrightarrow{H_2} H_2N\underset{\underset{NH}{\|}}{C}-NHNO + H_2O$$
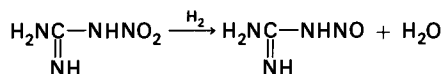
In a typical reduction, 10.4 gm nitroguanidine is suspended in 150 ml water with 0.5 gm platinum oxide. The reduction is carried out at atmospheric pressure or at 4 atm and stopped after absorption of one equivalent of hydrogen. The higher pressure gives a faster rate of reduction but the yield is not changed. The optimum temperature is 25–35°C; lower rates of reduction are found at both higher and lower temperatures (Lieber and Smith, 1935).

D. Azo-, Hydrazo-, and Azoxybenzenes

Azoxybenzenes may be formed by hydrogenation of aromatic nitro compounds. For instance, reduction of 4-nitro-2-chlorobenzoic acid over 5% palladium-on-barium sulfate in isopropanol ceased after absorption of 1.9 equivalents of hydrogen and gave 3,3'-dichloroazoxybenzene-4,4'-dicarboxylic acid. Evidently formation of the azoxy compound was due to some deactivation of the catalyst, for in another experiment four equivalents of hydrogen were absorbed at constant rate and 4-aminobenzoic acid was obtained in 90% yield (Weizmann, 1949).
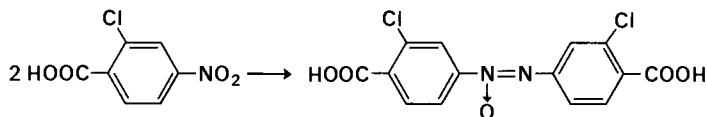
Reduction of o-nitrochlorobenzene over palladium or platinum in alkaline medium containing small amounts of 1,4-naphthoquinone or 1,4-naphthalenediol gave as the major product 2,2'-dichlorohydrazobenzene. A mixture consisting of 78.5 gm o-nitrochlorobenzene, 0.5 gm 5% palladium- or platinum-on-carbon, 1.0 gm 2,3-dichloro-1,4-naphthoquinone, 30 gm 50% aqueous sodium hydroxide, 100 ml water, and 1.0 gm sodium decylbenzenesulfonate, when reduced at 50–60°C at 50 psig until absorption had practically ceased, gave 57.0 gm 2,2'-dichlorohydrazobenzene. If the naphthalene compound is omitted from the reaction mixture the yield of dichlorohydrazobenzene is very low (Werner et al., 1964). Azoxy- and azobenzenes
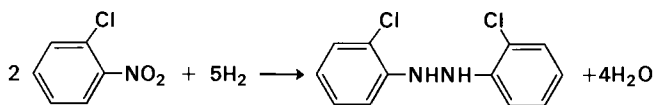
have also been formed by reductions using hydrazines as a source of hydrogen. Reduction of nitrobenzene with hydrazine and a 1% palladium-on-calcium carbonate catalyst gave azoxybenzene when the solvent was ethanolic potassium hydroxide, and azobenzene when the solvent was methanolic potassium hydroxide (Busch and Schulz, 1929). Good yields of hydrazo

compounds have been obtained by reduction of aromatic nitro compounds with hydrazine in 5% potassium hydroxide solution over 5% palladium-on-carbon and preferably 5% ruthenium-on-carbon (Pietra and Res, 1958). Formation of azobenzenes by catalytic hydrogenation of nitro compounds is favored by alkaline media, as it is in chemical reductions. Both organic and inorganic alkaline materials have been used (Freed and Signaigo, 1944).

REFERENCES

Abu-Mustafa, E. A., and Fayez, M. B. E., *J. Org. Chem.* **26**, 161 (1961).
Adams, R., and Cohen, F. L., *in* "Organic Syntheses," Collected Vol. I (Gilman, H., and Blatt, A. H., ed), p. 240. Wiley, New York, 1941.
Adams, R., Cohen, F. L., and Rees, C. W., *J. Am. Chem. Soc.* **49**, 1093 (1927).
Armarego, W. L. F., *J. Chem. Soc.* p. 5030 (1962).
Baer, H. H., and Achmatowicz, B., *J. Org. Chem.* **29**, 3180 (1964a).
Baer, H. H., and Achmatowicz, B., *Angew. Chem. Intern. Ed. English* **3**, 224 (1964b).
Baer, H. H., and Fischer, H. O. L., *J. Am. Chem. Soc.* **82**, 3709 (1960).
Baker, B. R., and Jordaan, J. H., *J. Med. Chem.* **8**, 35 (1965).
Baltzly, R., and Phillips, A. P., *J. Am. Chem. Soc.* **68**, 261 (1946).
Barker, R., *J. Org. Chem.* **29**, 869 (1964).
Bauer, K. H., *Chem. Ber.* **71B**, 2226 (1938).
Benington, F., Morin, R. D., and Clark, L. C., Jr., *J. Org. Chem.* **25**, 1542 (1960).
Benner, R. G., and Stevenson, A. C., U.S. Patent 2,619,503, Nov. 25, 1952.
Bergmann, E. D., and Blum, J., *J. Org. Chem.* **26**, 3214 (1961).
Berse, C., Boucher, R., and Piché, L., *J. Org. Chem.* **22**, 805 (1957).
Blackwood, R. K., Hess, G. B., Larrabee, C. E., and Pilgrim, F. J., *J. Am. Chem. Soc.* **80**, 6244 (1958).
Blood, A. E., and Noller, C. R., *J. Org. Chem.* **22**, 711 (1957).
Bruce, W. F., and Perez-Medina, L. A., *J. Am. Chem. Soc.* **69**, 2571 (1947).
Brunner, W. H., and Halasz, A., U.S. Patent 3,088,978, May 7, 1963.
Busch, M., and Schulz, K., *Chem. Ber.* **62B**, 1458 (1929).
Clendinning, R. A., and Rauscher, W. H., *J. Org. Chem.* **26**, 2963 (1961).
Clinton, R. O., and Laskowski, S. C., *J. Am. Chem. Soc.* **74**, 2226 (1952).
Controulis, J., Rebstock, M. C., and Crooks, H. M., Jr., *J. Am. Chem. Soc.* **71**, 2463 (1949).
Daly, J., Horner, L., and Witkop, B., *J. Am. Chem. Soc.* **83**, 4787 (1961).
Davis, A. L., Lloyd, R., Fletcher, J., Bayliss, L., and McCord, T. J., *Arch. Biochem. Biophys.* **102**, 48 (1963).
Davis, A. L., Choun, O. H. P., Cook, D. E., and McCord, T. J., *J. Med. Chem.* **7**, 632 (1964).
Dewar, M. J. S., and Mole, T., *J. Chem. Soc.* p. 2556 (1956).
Dietzler, A. J., and Keil, T. R., U.S. Patent 3,051,753, Aug. 28, 1962.
Dovell, F. S., and Greenfield, H., *J. Am. Chem. Soc.* **87**, 2767 (1965).
Dyumaev, K. M., and Belostotskaya, I. S., *Zh. Obshch. Khim.* **32**, 2661 (1962).
Fanta, P. E., *J. Am. Chem. Soc.* **75**, 737 (1953).
Feldstein, R., Aldridge, M. H., and Alexander, B. H., *J. Org. Chem.* **26**, 1656 (1961).
Fidler, D. A., Logan, J. S., and Boudakian, M. M., *J. Org. Chem.* **26**, 4014 (1961).
Fieser, L. F., and Joshel, L. M., *J. Am. Chem. Soc.* **62**, 1211 (1940).
Foster, R. E., and Kirby, A. F., U.S. Patent 2,967,200, Jan. 3, 1961.
Freed, W. V., and Signaigo, F. K., U.S. Patent 2,344,244, Mar. 14, 1944.
Freifelder, M., and Robinson, R. M., U.S. Patent 3,079,435, Feb. 26, 1963.

Freifelder, M., Martin, W. B., Stone, G. R., and Coffin, E. L., *J. Org. Chem.* **26**, 383 (1961).

Gardner, C., and French, G. P., British Patent 852,144, Oct. 26, 1960.

Garreau, Y., *Compt. Rend.* **222**, 963 (1946).

Goldkamp, A. H., U.S. Patent 3,125,589, Mar. 17, 1964.

Grabiel, C. E., Bisgrove, D. E., and Clapp, L. B., *J. Am. Chem. Soc.* **77**, 1293 (1955).

Green, M., U.S. Patent 3,062,884, Nov. 6, 1962.

Hafner, L. S., and Evans, R., *J. Am. Chem. Soc.* **79**, 3783 (1957).

Harris, S. A., and Folkers, K., *J. Am. Chem. Soc.* **61**, 1245 (1939).

Harris, S. A., Stiller, E. T., and Folkers, K., *J. Am. Chem. Soc.* **61**, 1242 (1939).

Heacock, R. A., Hutzinger, O., Scott, B. D., Daley, J. W., and Witkop, B., *J. Am. Chem. Soc.* **85**, 1825 (1963).

Hein, F., and Wagner, F., *Chem. Ber.* **68B**, 856 (1935).

Hernandez, L., and Nord, F. F., *Experientia* **3**, 489 (1947).

Hernandez, L., and Nord, F. F., *J. Colloid Sci.* **3**, 363 (1948).

Holley, R. W., and Holley, A. D., *J. Am. Chem. Soc.* **74**, 3069 (1952).

Huebner, C. F., and Link, K. P., *J. Am. Chem. Soc.* **67**, 99 (1945).

Huebner, C. F., Troxell, H. A., and Schroeder, D. C., *J. Am. Chem. Soc.* **75**, 5887 (1953).

Iffland, D. C., and Cassis, F. A., Jr., *J. Am. Chem. Soc.* **74**, 6284 (1952).

Jackman, L. M., *Advan. Org. Chem.* **2**, 329 (1960).

Joris, G. G., U.S. Patent 2,969,393, Jan. 24, 1961.

Joris, G. G., and Vitrone, J., Jr., U.S. Patent 2,829,163, Apr. 1, 1958.

Kahr, K., and Zimmerman, K., Swiss Patent 325,080, Dec. 14, 1957.

Karpenko, I., Unpublished observations, Engelhard Ind., 1960.

Kaye, I. A., and Roberts, I. M., *J. Am. Chem. Soc.* **73**, 4762 (1951).

Kindler, K. E., Brandt, E., and Gehlhaar, E., *Ann. Chem. Liebigs* **511**, 209 (1934).

Kindler, K., Oelschläger, H., and Henrich, P., *Chem. Ber.* **86**, 167 (1953).

Klemm, L. H., Sprague, J. W., and Mak, E. Y. K., *J. Org. Chem.* **22**, 161 (1957).

Kloetzel, M. C., *J. Am. Chem. Soc.* **69**, 2271 (1947).

Kohler, E. P., and Drake, N. L., *J. Am. Chem. Soc.* **45**, 1281 (1923).

Kornblum, N., and Fishbein, L., *J. Am. Chem. Soc.* **77**, 6266 (1955).

Kuhn, L. P., *J. Am. Chem. Soc.* **73**, 1510 (1951).

Leonard, N. J., and Beck, K. M., *J. Am. Chem. Soc.* **70**, 2504 (1948).

Leonard, N. J., Hruda, L. R., and Long, F. A., *J. Am. Chem. Soc.* **69**, 690 (1947).

Lieber, E., and Smith, G. B. L., *J. Am. Chem. Soc.* **57**, 2479 (1935).

Lieber, E., and Smith, G. B. L., *J. Am. Chem. Soc.* **58**, 2170 (1936).

Lonchamp, D., and Baumgartner, P., *Compt. Rend.* **257**, 668 (1963).

Love, R. F., *J. Org. Chem.* **29**, 366 (1964).

Luvisi, J. P., U.S. Patent 3,150,185, Sept. 22, 1964.

McWhorter, J. R., Jr., U.S. Patent 3,173,953, Mar. 16, 1965.

Makino, K., and Takahashi, H., *J. Am. Chem. Soc.* **76**, 4994 (1954).

Masamune, T., Takasugi, M., Suginome, H., and Yokoyama, M., *J. Org. Chem.* **29**, 681 (1964).

Meister, H., and Franke, W., U.S. Patent 2,886,596, May 12, 1959.

Moll, H., Musso, H., and Schröder, H., *Angew. Chem. Intern. Ed. English* **2**, 212 (1963).

Munk, M., and Schultz, H. P., *J. Am. Chem. Soc.* **74**, 3433 (1952).

Nielsen, A. T., *J. Org. Chem.* **27**, 1998 (1962).

Neilson, T., Wood, H. C. S., and Wylie, A. G., *J. Chem. Soc.* p. 371 (1962).

Ölschläger, H., *Chem. Ber.* **89**, 2025 (1965).

Papesch, V., U.S. Patent 3,056,781, Oct. 2, 1962.

Parker, E. D., and Shive, W., *J. Am. Chem. Soc.* **69**, 63 (1947).

Parrett, A. N., and Lowy, A., *J. Am. Chem. Soc.* **48**, 778 (1926).

Phillips, A. P., and Maggiolo, A., *J. Org. Chem.* **15**, 659 (1950).

Pietra, S., and Res, M., *Ann. Chim. (Rome)* **48**, 299 (1958).

Reichert, B., and Koch, W., *Arch. Pharm.* **273**, 265 (1935).

Reichert, B., and Marquardt, H., *Pharmazie* **5**, 10 (1950).

Roberts, J. D., Lee, C. C., and Saunders, W. H., Jr., *J. Am. Chem. Soc.* **76**, 4501 (1954).

Robertson, J. A., *J. Org. Chem.* **13**, 395 (1948).

Roblin, R. O., Jr., and Winnek, P. S., *J. Am. Chem. Soc.* **62**, 1999 (1940).

Ross, S. D., and Kuntz, I., *J. Am. Chem. Soc.* **74**, 1297 (1952).

Rupe, H., and Vogler, H., *Helv. Chim. Acta* **8**, 832 (1925).

Rylander, P. N., Rakoncza, N., Steele, D., and Bolliger, M., *Engelhard Ind. Tech. Bull.* **4**, 95 (1963).

Rylander, P. N., Kilroy, M., and Coven, V., *Engelhard Ind. Tech. Bull.* **6**, 11 (1965).

Schipper, E., Chinery, E., and Nichols, J., *J. Org. Chem.* **26**, 4145 (1961).

Schmidt, E., Ascherl, A., and Mayer, L., *Chem. Ber.* **58B**, 2430 (1925).

Schulenberg, J. W., and Archer, S., *J. Org. Chem.* **30**, 1279 (1965).

Seifert, W. K., and Condit, P. C., *J. Org. Chem.* **28**, 265 (1963).

Sonn, A., and Schellenberg, A., *Chem. Ber.* **50**, 1513 (1917).

Southwick, P. L., and Casanova, J., Jr., *J. Am. Chem. Soc.* **80**, 1168 (1958).

Spiegler, L., U.S. Patent 2,765,342, Oct. 2, 1956.

Spiegler, L., U.S. Patent 3,073,865, Jan. 15, 1963.

Taya, K., *Sci. Papers Inst. Phys. Chem. Res. (Tokyo)* **56**, 285 (1962).

Taylor, T. W. J., and Baker, W., *In* "Sidgwick's Organic Chemistry of Nitrogen" (N. V. Sidgwick, ed.), p. 163. Oxford Univ. Press (Clarendon), London and New York, 1945.

Titov, A. I., and Baryshnikova, A. N., *Zh. Obshch. Khim.* **23**, 346 (1953).

Truitt, P., Hall, B., and Arnwine, B., *J. Am. Chem. Soc.* **74**, 4552 (1952).

Vavon, G., and Krajcinovic, M., *Compt. Rend.* **187**, 420 (1928).

Vorozhtsov, N. N., Yakobson, G. G., and Denisova, L. I., *Zh. Obshch. Khim.* **31**, 1222 (1961).

Walker, G. N., *J. Am. Chem. Soc.* **77**, 3844 (1955).

Weinmayr, V., *J. Am. Chem. Soc.* **77**, 1762 (1955).

Weise, J., German Patent 917,426, Sept. 2, 1954.

Weizmann, A., *J. Am. Chem. Soc.* **71**, 4154 (1949).

Werner, R. E., Young, N., Prichett, J. J., and Brenner, C. E., U.S. Patent 3,156,724, Nov. 10, 1964.

Wheatley, W. B., Fitzgibbon, W. E., Jr., and Cheney, L. C., *J. Am. Chem. Soc.* **76**, 4490 (1954).

Whitman, G. M., U.S. Patent 2,606,925, Aug. 12, 1952.

Yao, H.-C., and Emmett, P. H., *J. Am. Chem. Soc.* **81**, 4125 (1959).

Yao, H.-C., and Emmett, P. H., *J. Am. Chem. Soc.* **83**, 796 (1961a).

Yao, H.-C., and Emmett, P. H., *J. Am. Chem. Soc.* **83**, 799 (1961b).

Young, D. V., and Snyder, H. R., *J. Am. Chem. Soc.* **83**, 3161 (1961).

Young, V. V., U.S. Patent 2,864,863, Dec. 16, 1958.

12

Nitriles

Catalytic hydrogenation of nitriles may give rise to a number of products, which include primary, secondary, and tertiary amines, imines, hydrocarbons, aldehydes, amides, and alcohols. The major product, derived as a resultant of several competing reactions, depends importantly on the catalyst, substrate, and reaction conditions. Primary amines, which usually are the goal of a nitrile reduction, are formed to the extent that other competing reactions, notably coupling reactions leading to secondary and tertiary amines, can be avoided.

I. COUPLING REACTIONS: SECONDARY AND TERTIARY AMINES

The formation of secondary and tertiary amines, as well as certain hydrolysis products, in nitrile hydrogenations is usually accounted for by the assumption of an imine intermediate (von Braun et al., 1923):

$$RC \equiv N \xrightarrow{H_2} RCH=NH \xrightarrow{H_2} RCH_2NH_2$$
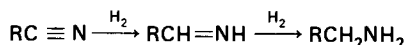
Addition of the primary amine to the intermediate imine gives a product from which the secondary amine may be formed by hydrogenolysis,

$$RCH=NH + RCH_2NH_2 \rightleftharpoons RCH(NH_2)NHCH_2R$$

$$RCH(NH_2)NHCH_2R \xrightarrow{H_2} (RCH_2)_2NH + NH_3$$
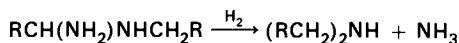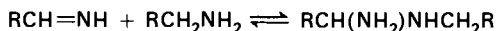
or by elimination of ammonia followed by hydrogenation:

$$RCH=NH + RCH_2NH_2 \rightleftharpoons RCH=NCH_2R + NH_3$$

$$RCH=NCH_2R + H_2 \longrightarrow (RCH_2)_2NH$$
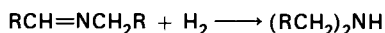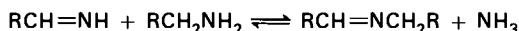
Tertiary amines may be formed similarly through addition of a secondary amine to an imine followed by hydrogenolysis. Minor variations of this general scheme have been proposed by other workers (Mignonac, 1920;

Winans and Adkins, 1932; Juday and Adkins, 1955). Imines may at times
be the major product. Hydrogenation of 30 gm 4-phenyl-4-cyano-*N*-
methylpiperidine (I) over palladium-on-carbon in ethanol gave after
distillation 16 gm bis[(4-phenyl-*N*-methyl-4-piperidyl)methyl]imine (II)
(Chiavarelli and Marini-Bettolo, 1956).
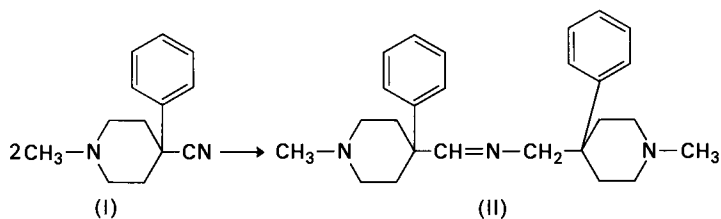
Primary amines will be formed if the sequence of reactions leading to
secondary and tertiary amines can be broken. One way of preventing the
addition reaction between the primary amine and imine is to remove effect-
ively the primary amine from the system as it is formed, as by salt formation
or by acylation. Another way is by carrying out the reduction in the presence
of ammonia. (These techniques are discussed more fully in the section below
on solvents.)

It is possible that the yield of primary amine may decrease if the reduction
is continued after all unsaturation has been removed. For instance, hydro-
genation of benzylamine over palladium in ethanol gives almost quantitative
yields of dibenzylamine. The reduction is believed to proceed through an
imine intermediate (Kindler *et al.*, 1931).
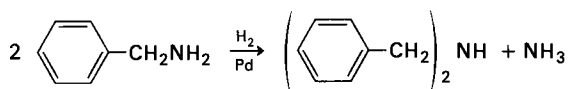
Stegemeyer (1946) has disclosed a method of decreasing the formation of
secondary amines by adding secondary amines, formed in previous re-
actions, to the mixture undergoing hydrogenation. For instance, the yield
of octadecylamine was increased from 64% to 84% by carrying out the
reduction in the presence of secondary amines formed in previous reductions.

The reaction scheme outlined above has certain implied consequences
that have been turned to good advantage. Kindler and Hesse (1933) pointed
out that, since secondary and tertiary amines as well as primary amines were
formed in the reduction of nitriles, it should be possible to prepare various
secondary and tertiary amines by hydrogenating a nitrile in the presence of
an added amine:

$$RCN + R'NH_2 \longrightarrow RCH_2NHR' + NH_3$$

$$RCN + R_2'NH \longrightarrow RCH_2NR_2' + NH_3$$
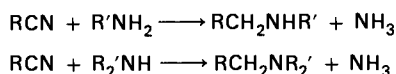
The procedure was applied, for instance, to the synthesis of *N*-substituted phenylethylamines by hydrogenation of a mixture of a benzyl cyanide and an amine (Kindler *et al.*, 1950):

$$O_2N-\!\!\!\left\langle\!\!\!\bigcirc\!\!\!\right\rangle\!\!\!-CH_2CN + (CH_3)_2NH \xrightarrow[C_2H_5OH]{5\%Pd/BaSO_4} H_2N-\!\!\!\left\langle\!\!\!\bigcirc\!\!\!\right\rangle\!\!\!-CH_2CH_2N(CH_3)_2$$
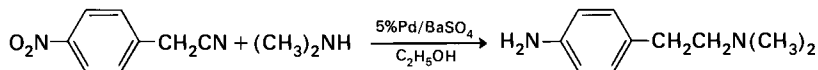
A mixture of platinum oxide and palladium oxide has been used also as a catalyst in this type of reductive condensation (Saito *et al.*, 1956).

A. SOLVENTS

The solvent is of considerable importance in determining the course and rate of nitrile hydrogenation. Hydrogenation of nitriles in neutral media frequently affords mixtures of primary, secondary, and tertiary amines. The extent of coupling also depends on the structure of the substrate. With unhindered, low molecular weight nitriles only secondary and tertiary amines may be formed in neutral media, as in the hydrogenation of propionitrile (discussed at length in the section on catalysts). On the other hand, larger nitriles may give fair yields of primary amine even in neutral solution. For instance, 6-aminomethylpurine was obtained in 75% yield by hydrogenation of 6-cyanopurine over 5% palladium-on-carbon in methanol (Giner-Sorolla and Bendich, 1958).

1. *Acidic Media*

Hartung (1928) pointed out that secondary amine formation could be prevented or minimized by carrying out hydrogenations in alcohol in the presence of mineral acid. For instance, only benzylamine was formed by hydrogenation of benzonitrile over palladium-on-carbon in absolute ethanol containing at least one equivalent of hydrogen chloride, whereas without hydrogen chloride a mixture of benzylamine, dibenzylamine, and ammonia was formed. Earlier workers (Rosenmund and Pfannkuch, 1923) had observed that nitrile reductions over palladium in acetic acid were accelerated and the yield of primary amine increased by addition of dry hydrogen chloride or concentrated sulfuric acid. Carboxylic acids without mineral acid present are not strong enough to prevent secondary amine formation. For instance, more secondary amine was formed in hydrogenation of *p*-tolunitrile in acetic acid (84% yield) than in ethanol (67% yield). In other comparisons acetic acid appears to somewhat better advantage. Only 38% secondary amine was formed on reduction of benzonitrile over platinum oxide in acetic acid whereas 79% was formed in ethanol (Carothers and Jones, 1925).

An example of the use of mineral acid in preventing secondary amine formation is the hydrogenation of ethyl α,γ-dicyanobutyrate (III) to α-aminomethyl-δ-aminovaleric acid (IV). The reduction was carried out over 0.2 gm platinum oxide with 0.01 mole of ethyl α,γ-dicyanobutyrate dissolved in 15 ml acetic acid containing 1.0 gm concentrated sulfuric acid. The theoretical amount of hydrogen was absorbed in 5 hours (van Tamelen and Smissman, 1953). This substrate might be expected to be unusually difficult to reduce without extensive secondary amine formation, because either inter- or intra-molecular coupling could occur. Piperidines are formed by reduction of glutaronitriles in ethanol (Bergel *et al.*, 1948).

$$NCCH_2CH_2\underset{\underset{CN}{|}}{C}HCOOC_2H_5 \xrightarrow[\text{(2)}H_2O]{\text{(1)}H_2} H_2NCH_2CH_2CH_2\underset{\underset{CH_2NH_2}{|}}{C}HCOOH$$

(III)   (IV)
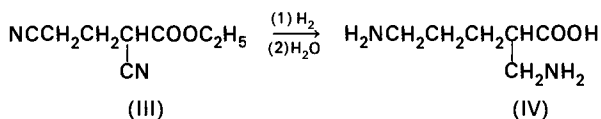
An example of the use of ethanol–hydrogen chloride in promoting primary amine formation is the preparation of trifluoromethylbenzylamines by hydrogenation of the corresponding benzonitriles (Freifelder and Ng, 1965). In one experiment, 17.1 gm 4-trifluoromethylbenzonitrile (0.1 mole) dissolved in 200 ml ethanol containing 0.3 mole of hydrogen chloride (or an equivalent amount of concentrated hydrochloric acid) was hydrogenated over 6.0 gm 5% palladium-on-carbon at 2 atm pressure. The reduction was complete in less than 1 hour and 4-trifluoromethylbenzylamine was isolated as the hydrochloride in 80% yield. The *ortho* isomer required 24 hours for complete reduction, probably because of steric effects.

$$CF_3\text{---}\langle\rangle\text{---}CN \longrightarrow CF_3\text{---}\langle\rangle\text{---}CH_2NH_2$$
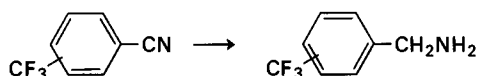
Formamidine was prepared in 95% yield by partial hydrogenation of cyanamide in dilute sulfuric acid or hydrochloric acid:

$$NH_2CN + H_2 \longrightarrow NH_2CH{=}NH$$
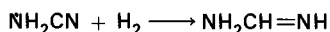
The reduction is especially interesting because of the technique used. Twenty grams of 1.4% palladium-on-carbon in 200 ml water was prereduced in a reaction flask provided with two separatory funnels and a stream of flowing hydrogen. After prereduction, 100 ml 12% sulfuric acid or 100 ml 9% hydrochloric acid was added to the flask from one funnel. An aqueous solution of 11 gm freshly prepared cyanamide in 100 ml water was added from the other funnel portionwise, 1.5 ml every 3 minutes. The theoretical amount of hydrogen was absorbed about 10 minutes after addition of the last portion (Odo *et al.*, 1957).

Some nitriles are not reduced satisfactorily in acidic media. Huber (1944) hydrogenated 4-amino-2-methyl-5-pyrimidinecarbonitrile over palladium-on-zirconium oxide, palladium-on-carbon, and platinum oxide in acetic

anhydride and in ethanol or acetic acid containing hydrochloric or sulfuric acid. In every case the secondary amine was an important or predominant product. He concluded that basic nitriles cannot be hydrogenated to the corresponding primary amines in good yields by methods involving the use of acidic solvents and palladium or platinum catalysts. Hydrogenation over Raney nickel in the presence of ammonia gave the primary amine in nearly quantitative yield (Huber, 1944). Later workers obtained hydrolysis products by hydrogenation over 10% palladium-on-carbon in acetic acid–hydrochloric acid (Miyatake and Tsunoo, 1952).

2. Acid Anhydride Solvents

Formation of secondary and tertiary amines during hydrogenation of nitriles may be prevented by carrying out the reaction in an acid anhydride solvent, a technique first described by Carothers and Jones (1925). The anhydride acylates the primary amine as it is formed and protects it against further reaction. For instance, hydrogenation of p-tolunitrile in acetic anhydride over platinum oxide afforded p-methylbenzylamine in 88% yield. When the solvent for this reduction was ethanol or acetic acid the primary amine was obtained in only 33% and 4% yields, respectively. Hydrogenation of p-tolunitrile in n-butyric anhydride afforded n-butyryl-p-methylbenzyl-amine in 74% yield:

$$(RCO)_2O + R'CN \xrightarrow{H_2} RCONHCH_2R' + RCOOH$$
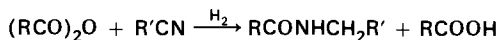
Carothers and Jones (1925) reported that the rate of reduction increased rapidly with temperature and so did the tendency for the catalyst to become poisoned. They suggested that in most reductions the optimum temperature is probably 30–50°C. Deactivated catalysts could not be reactivated by shaking with air. They found it desirable, frequently, to flush the hydrogen reservoir to prevent accumulation of poisons. The catalyst was used more economically, if it were added in two portions.

Hydrogenations in acetic anhydride often proceed slowly but the results are usually good. Overberger and Mulvaney (1959) obtained 2-(4-methyl-cyclohexyl)ethylamine (VI) by hydrogenation of p-xylyl cyanide (V) in acetic anhydride, hydrolysis to the amine, and further reduction. Numerous attempts to prepare VI in a single step by hydrogenation of V all failed. Two
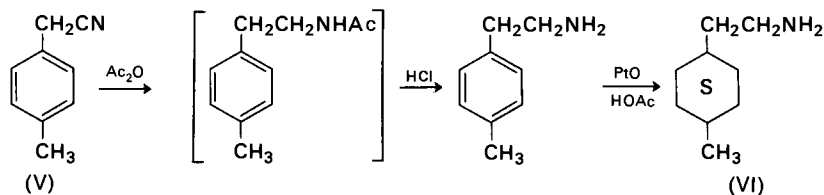
catalyst charges and a lengthy reduction time were required for a successful reduction. The reduction was carried out with 45 gm p-xylyl cyanide (0.34 mole) in 120 ml acetic anhydride over 2.2 gm platinum oxide added in two portions. After 48 hours the reaction mixture had absorbed 0.75 mole of hydrogen. The free amine was obtained in 70% yield after hydrolysis and distillation. Hydrogen absorption in excess of theoretical was probably due to slow reduction of the acetic anhydride solvent (Musso and Figge, 1962).

The photodimer of fumaronitrile, $cis,trans,cis$-1,2,3,4-tetracyanocyclo-butane (VII) was reduced successfully in acetic anhydride over platinum oxide to $cis,trans,cis$-1,2,3,4-tetra(acetamidomethyl)cyclobutane (VIII) after attempted reductions with lithium aluminum hydride failed. With 8.0 gm substrate and 0.7 gm platinum oxide the reduction took 1 week at 40 psig and 25°C (Griffin $et\ al.$, 1962).
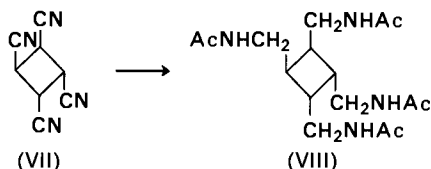
Reductions in acetic anhydride have also been carried out under more vigorous conditions. Perfluoroadiponitrile was reduced to the corresponding acetylated diamine over platinum oxide in acetic anhydride-ether at 1000 psig and 100°C (McBee and Wiseman, 1950).

$$NC(CF_2)_4CN \xrightarrow[H_2]{Ac_2O} (CF_2)_4(CH_2NHAc)_2$$
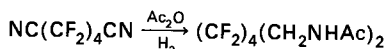
3. Ammonia

Hydrogenation of nitriles may be carried out with advantage in solutions containing excess ammonia. The ammonia presumably prevents or mini-mizes secondary or tertiary amine formation by removing the imine inter-mediate from the reaction mixture:

$$RCN \xrightarrow{H_2} RCH{=}NH \underset{NH_2}{\overset{NH_3}{\rightleftharpoons}} R\overset{|}{C}HNH_2 \xrightarrow{H_2} RCH_2NH_2 + NH_3$$
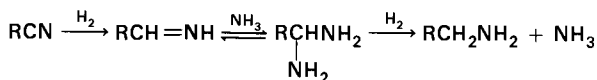
For example, tryptamine (X) was obtained in 78% yield by hydrogenation of 0.15 mole of 3-indoleacetonitrile (IX) in 170 ml 10% ethanolic ammonia (1.0 mole) over 4 gm 5% rhodium-on-alumina. Hydrogen absorption was
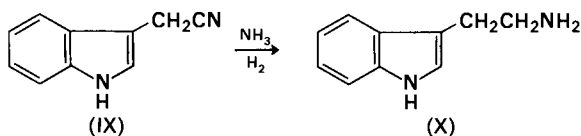
complete in less than 2 hours. In contrast, hydrogenation of 0.14 mole of 3-indoleacetonitrile over 4.4 gm 5% rhodium-on-alumina in 100 ml methanol containing no ammonia afforded very little tryptamine. The major product was bis(β-3-indolylethyl)amine (Freifelder, 1960).

Fifteen other aliphatic nitriles, including some β-cyanoethyl ethers and α-aminonitriles, classes of compounds readily susceptible to hydrogenolysis, were reduced by the above procedure with good results. Because of the ease of reduction and because of the good results with various sensitive compounds, Freifelder (1960) considered this procedure the one of choice. However, when applied to benzonitrile the results were not so satisfactory, as 30% dibenzylamine was formed (Freifelder and Ng, 1965).

B. CATALYSTS

The catalyst may be of decisive influence on the extent of coupling in a nitrile hydrogenation (Rylander and Steele, 1965). In a study of the effect of catalyst, propionitrile and benzonitrile in hexane were reduced over 5% palladium-, 5% platinum-, 5% rhodium-, and 5% ruthenium-on-carbon; the results are shown in Table I. The effect of catalyst on the product was

TABLE I

HYDROGENATION OF PROPIONITRILE AND BENZONITRILE[a]

Compound	Catalysts							
	5% Pd/C		5% Pt/C		5% Rh/C		5% Ru/C	
	Conv.	Yield	Conv.	Yield	Conv.	Yield	Conv.	Yield
Propionitrile	93[b]	—	32[b]	—	100	—	0	—
Propylamine	0	0	0	0	3	3	0	0
Dipropylamine	0	0	0	0	89	89	0	0
Tripropylamine	74	84	21	67	0	0	0	0
Benzonitrile	100	—	60[b]	—	100[c]	—	0	—
Benzylamine	52	52	3	5	13[c]	13	0	0
Dibenzylamine	49	49	58	96	33[c]	33	0	0
Tribenzylamine	0	0	0	0	0	0	0	0

[a] Temperature 25°C, pressure 50 psig (for propionitrile) and 500 psig (for benzonitrile). Catalyst, 300 mg; solvent, 50 ml hexane; and 0.1 mole of nitrile. *Note*: The reductions were continued until they spontaneously stopped. As indicated, some reductions ceased short of completion due to catalyst poisoning. Conversion refers to the percent of substrate reduced and to the percent of each product based on substrate charged. Yield refers to the percent of product based on substrate reduced.

[b] Reduction stopped spontaneously before completion.

[c] Strong imine absorption found in infrared.

marked. In hydrogenation of propionitrile, condensed products predominated; dipropylyamine was formed in high yield when rhodium-on-carbon was the catalyst, and tripropylamine when palladium or platinum was used. The formation of secondary or tertiary amine is unrelated to the rate of reduction of the nitrile. Rate data for hydrogenation of propionitrile in hexane, acetic acid, and water are given in Table II. Semiquantitative measurements of the products formed by hydrogenation in water and in acetic acid indicated the distribution of amines to be substantially the same as in hexane (Rylander and Kaplan, 1960).

TABLE II

HYDROGENATION OF PROPIONITRILE: EFFECT OF SOLVENT ON RATE[a]

Catalyst	Amount (mg)	Time (minutes) for absorption of one equivalent of hydrogen		
		Hexane	Acetic acid	Water
5 % Pd/C	300	195	30	290
	900	52	8	95
5 % Pt/C	300	525	570	335
	900	150	53	80
5 % Rh/C	300	350	36	280
	900	130	12	62

[a] 1.55 gm propionitrile and 100 ml solvent at room temperature and atmospheric pressure.

Propionitrile in hexane was reduced over palladium-, platinum-, rhodium-, and ruthenium-on-carbon under a number of other reaction conditions, but the product composition did not change greatly from that given in Table I. Reductions were carried out at pressures ranging to 1000 psig and temperatures to 150°C. The most significant change occurred with rhodium, which at 150°C and 500 psig afforded 19 % tripropylamine and 81 % dipropylamine. The products obtained in propionitrile hydrogenation were also shown to be virtually independent of both the amount of catalyst and the catalyst support. Of all variables studied, the catalytic metal had by far the greatest effect on the product.

These catalysts had a marked influence also on the products obtained in hydrogenation of benzonitrile, affording a distribution of amines that differed sharply from that obtained from propionitrile. Platinum catalysis gave a high yield of dibenzylamine, whereas palladium produced about equal amounts of benzyl- and dibenzylamine. The yield of amines obtained over rhodium was low, presumably due to formation of imines (identified only by infrared spectra). No tertiary amine was formed in any reduction.

TABLE III

HYDROGENATION OF PROPIONITRILE IN THE PRESENCE OF ADDED AMINE[a]

Catalyst	Moles of reactant			Change in moles on hydrogenation			
	Propio-nitrile	Propyl-amine	Dipropyl-amine	Δ Propio-nitrile	Δ Propyl-amine	Δ Di-propyl amine	Δ Tri-propyl-amine
5% Pd/C	0.1	0.1	0	−0.008[b]	+0.008	0	0
	0.1	0	0.1	0.1	0	−0.1	+0.1
5% Pt/C	0.1	0.1	0	−0.05[b]	−0.05	+0.05	0
	0.1	0	0.1	−0.03[b]	+0.01	−0.02	+0.02
5% Rh/C	0.1	0.1	0	−0.1	0	+0.1	0
	0.1	0	0.1	−0.1	0	+0.05	0

[a] 300 mg catalyst and 50 ml hexane at 25°C and 50 psig.
[b] Reduction stopped spontaneously before completion.

Table III gives data on the effect of catalyst on the coupling reactions:

$$CH_3CH_2CN + CH_3CH_2CH_2NH_2 \xrightarrow{H_2} (CH_3CH_2CH_2)_2NH + NH_3$$

$$CH_3CH_2CN + (CH_3CH_2CH_2)_2NH \xrightarrow{H_2} (CH_3CH_2CH_2)_3N + NH_3$$
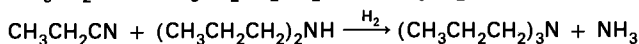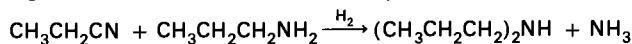
Hydrogenation of equimolar amounts of propionitrile and propylamine over rhodium or platinum resulted only in formation of dipropylamine. Palladium was poisoned quickly in this reaction mixture. The differences among the catalysts were accentuated when the substrate was an equimolar mixture of propionitrile and dipropylamine. Over rhodium, only more dipropylamine was formed; there was no tripropylamine. On the other hand, only tripropylamine was formed over palladium, and the dipropylamine disappeared. Over platinum, tripropylamine was formed together with some propylamine. Propylamine was apparently unable to compete successfully in this reduction, which did not go to completion, with the larger amount of dipropylamine present.

II. PRODUCTS OF REDUCTIVE HYDROLYSIS

Hydrogenation of nitriles carried out in aqueous media may give aldehydes derived by hydrolysis of intermediate aldimines. The aldehyde may then be reduced to an alcohol or may interact with an amine, forming a ketimine and water. Formation of ketimines by this sequence requires only catalytic amounts of water (Snyder et al., 1958). Hydrogenation of nitriles carried out in aqueous media in the presence of semicarbazide affords the semicarbazones

in 25–75 % yield (Plieninger and Werst, 1955). Hydrogenation of 5-chloro-valeronitrile in aqueous ethanol in the presence of semicarbazide gave 5-chlorovaleraldehyde semicarbazone in 47 % yield (Rogers, 1963).

The work of Miyatake and Tsunoo (1952) on 4-amino-2-methyl-5-pyrimidine-carbonitrile (XI) provides an illustration of the formation of alcohols by hydrogenation of nitriles. Hydrogenation of 15 gm XI in acetic acid–hydrochloric acid over 15 gm 10 % palladium-on-carbon gave 9 gm of the methylamine (XII) and 5 gm of the carbinol (XIII). When the hydro-genation was carried out over Raney nickel in neutral alcohol, the Schiff base, $C_{12}H_{15}N_7$, was formed from which the methylamine (XII) and the aldehyde (XIV) were formed by acid hydrolysis. No carbinol was formed in the neutral hydrogenation.
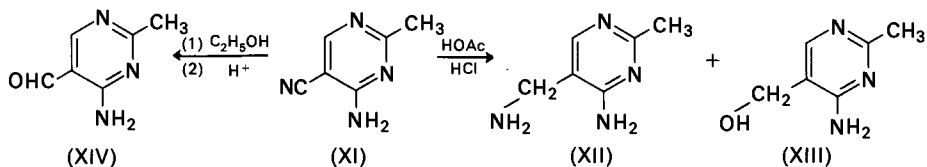
III. NITRILES WITH OTHER FUNCTIONAL GROUPS

Many nitriles contain another function, frequently one susceptible to hydrogenation or hydrogenolysis. The following sections, dealing with the hydrogenation of such molecules, are limited to examples where at least the nitrile function is reduced. (Hydrogenations in which the nitrile function remains unchanged are discussed in the chapter appropriate to the group reduced.)

A. CYANOHYDRINS

Cyanohydrins may be reduced in good yields to the corresponding amino alcohol. The reductions are usually carried out over platinum oxide, but this choice seems to stem more from well-established precedent than from a demonstrated superiority of this particular catalyst. Difficulties in the reduction may arise from instability of the cyanohydrin. For instance, hydrogenation of tropinone cyanohydrin (XV) to 3-aminomethyl-3-tropanol (XVI) gave satisfactory, reproducible yields only when the reduction was carried out immediately after purification of the substrate. Tropinone cyanohydrin (34.7 gm), purified by washing with water, alcohol, and ether followed by brief drying under reduced pressure, was dissolved in 350 ml glacial acetic acid and hydrogenated at 40°C over 1.0 gm prereduced platinum

oxide. Nearly two equivalents of hydrogen were absorbed in 4 hours. The amino alcohol was obtained in 72% yield (Cope *et al.*, 1950).

(XV)   (XVI)
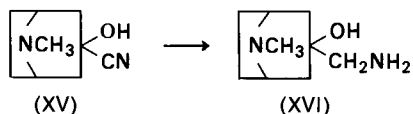
Other examples of reduction of cyanohydrins over platinum oxide in acetic acid have been given by House *et al.* (1960), Gutsche (1949), and Ringold (1960). Tchoubar (1949) has recommended the use of platinum oxide, partially poisoned by addition of carbon disulfide, for reduction in acetic acid of cycloalkanone cyanohydrins to the amino alcohols. The catalyst may also be suitably inhibited by traces of hydrogen cyanide or by hydrochloric acid.

1. *Hydrogenolysis of Cyanohydrins*

Cyanohydrins derived from aromatic aldehydes may suffer loss of the hydroxyl group as well as reduction of the cyano function. For instance, Hartung (1928) was unable to obtain phenylethanolamine on reduction of mandelonitrile over palladium-on-carbon in ethanol–hydrogen chloride even when absorption was limited to two equivalents of hydrogen; the products were phenylethylamine, isolated in 52% yield, and an unidentified nonbasic by-product. Similarly, catalytic hydrogenation of 3,4-diethoxymandelonitrile over platinum oxide in ethanol–hydrochloric acid afforded β-(3,4-diethoxyphenyl)ethylamine in 42% yield (Weijlard *et al.*, 1949). Buck (1933) showed the products obtained on reduction of a mandelonitrile to depend, at least in part, on the substituents. A number of mandelonitriles were reduced over platinum oxide in ethanol–hydrochloric acid; those nitriles with an *ortho* substituent were converted to the β-hydroxy-β-phenylethylamine, whereas those without an *ortho* substituent were converted to β-phenylethylamine. However, the benzyl alcohol group was partially preserved in hydrogenation of isovanillin cyanohydrin over 30% palladium-on-carbon in ethanol containing one equivalent of hydrogen chloride; α-(aminoethyl)-3-hydroxy-4-methoxybenzyl alcohol was obtained in 20% yield (Vinogradova and Arkhangel'skaya, 1946). Carbomethoxymandelonitriles were converted to β-phenylethylamines whether an *ortho* substituent was present or not (Buck, 1933).

B. AMINONITRILES

Catalytic hydrogenation of α-aminonitriles usually does not afford primary diamines. The difference between the rate of hydrogenation and the rate of hydrogenolysis is small, and extensive hydrogenolysis may occur

unless the amino group has an acyl substituent. Hydrogenation of α-amino-nitriles in acetic anhydride over platinum oxide has given excellent yields of the α,β-diacetamido compound. Hydrolysis of these compounds to the diamine can be readily accomplished unless a nitrogen is attached to a tertiary carbon, in which case a piperazine is the major product (Reihlen *et al.*, 1932). Alternatively, α-aminonitriles may be converted to diamines through hydrogenation of their monoacetyl derivatives followed by hydrolysis of the resulting dihydroimidazoles (Hawkins and Biggs, 1949). Acetylation also prevents the liberation of hydrogen cyanide, which may poison the catalyst (Reihlen *et al.*, 1932).

Freifelder and Hasbrouck (1960) have carried out successful low pressure reductions of unsubstituted α-aminonitriles in alcoholic hydrogen chloride over platinum oxide. Diamines are obtained directly without hydrolysis of the product. Typically, 235 ml 14% alcoholic hydrogen chloride (0.9 mole) was cooled in a Parr shaker bottle. The aminonitrile (0.3 mole) was added in portions while keeping the temperature below 10°C. Platinum oxide (1 gm) was added *carefully* and the mixture hydrogenated under 3 atm pressure. This low pressure procedure does not appear to be applicable to α-amino-nitriles in which the amino group is substituted. Extensive hydrogenolysis occurred during reduction of XVII to give methylamine hydrochloride in 89% yield and XVIII in 69% yield. Extensive hydrogenolysis also occurred during reduction of 1-dimethylamino-1-cyclohexanecarbonitrile and di-ethylaminoacetonitrile.
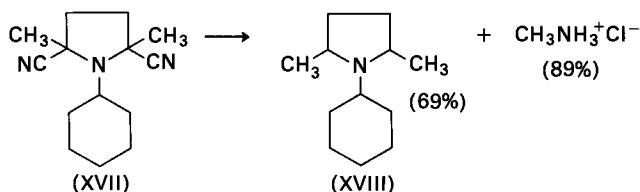
Strack and Schwaneberg (1932) reduced α-aminonitriles to the diamines over palladium sponge in alcohol–hydrogen chloride. They stress the importance of always keeping the solution acid, and favor carrying out the reduction as rapidly as possible by using large amounts of catalyst (which may be reused repeatedly). Freifelder (1960) converted at low pressure a series of aminonitriles to diamines, using 5% rhodium-on-alumina in the presence of alcoholic ammonia. When at least five equivalents of ammonia were used the yield of secondary amine was kept to low yields. The α-aminonitriles—4-methylpiperazinoacetonitrile and 1-piperidoacetonitrile—were reduced in alcoholic ammonia at low pressure to the corresponding diamines in yields of 92% and 78%, respectively. To facilitate isolation, dimethyl-aminoacetonitrile was hydrogenated in the presence of ammonia but without solvent at 1050 psig. The yield of β-dimethylaminoethylamine was

68%. At high pressure without solvent and without ammonia the yield dropped to 43%. Hydrogenation without solvent at low pressure was extremely slow. The rhodium–alcohol–ammonia procedure provides a needed supplement to the alcohol–hydrochloric acid–platinum oxide procedure (Freifelder and Hasbrouck, 1960), which proved unsatisfactory for reduction of N-substituted α-aminonitriles.

The β-, γ-, and δ-aminonitriles were also reduced over rhodium-on-alumina in alcoholic ammonia to give the corresponding diamines in 63–82% yield. The general procedure is the same as that given (page 208) for hydrogenation of 3-indoleacetonitrile (Freifelder, 1960).

1. Cyclizations

Suitably spaced aminonitriles may afford cyclic products on catalytic hydrogenation. The reduction probably proceeds in much the same way as intermolecular interaction of an amine and a nitrile. Aminonitriles are likely intermediates in the reductive cyclization of succinonitriles and glutaronitriles to pyrrolidines and piperidines. Hydrogenation of o-nitro-phenylacetonitriles leads to indoles, a reaction that proceeds through an o-aminophenylacetonitrile intermediate. The sequence leading to indoles is probably not fundamentally different from that leading to pyrrolidenes or piperidines, but unsaturation remains in the indole synthesis because of the well-established resistance of indoles to hydrogenation. Indoles are probably formed from o-nitrophenylacetonitriles by the following sequence (Snyder et al., 1958). The nitro group is rapidly reduced, followed by slow addition of one mole of hydrogen to the nitrile to form a β-o-aminoaryl-ethylimine. From this compound an indolenine could be formed by cyclization with intramolecular loss of ammonia, or by hydrolysis with catalytic amounts of water to an aldehyde that then cyclizes with formation of an indolenine and water. Tautomerization produces the indole. Another sequence, since retracted (Walker, 1965), was presented (page 189).
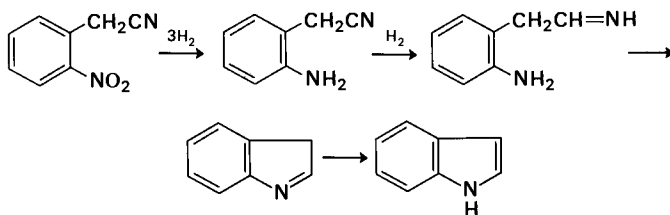
A synthesis of 1,3,4,5-tetrahydropyrrolo[4.3.2-de]quinoline (XX) involved reductive cyclization of 4-nitroindol-3-ylacetonitrile (XIX) in a reaction following substantially the same course as the indole synthesis described above. The author suggested that the hydrogenation proceeds stepwise

with an initial facile reduction of the nitro group to an amine (isolated as a by-product), reduction of the nitrile to an imine, and cyclization by interaction of the amine and imine, followed by loss of ammonia and saturation of the cyclic imine. The hydrogenation was carried out with 4.0 gm XIX, 2.0 gm 10% palladium-on-carbon, and 300 ml ethyl acetate at 45 psig. The reduction required 2.6 hours and the temperature was raised by external heating from about 25°C at the start of the reduction to 70°C at the end (Hester, 1964).

(XIX)   (XX)
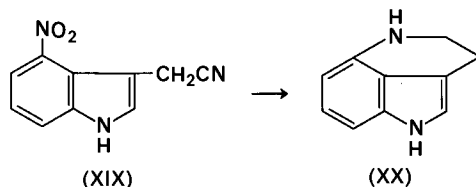
Indolizidine and quinolizidine derivatives have been obtained by reductive cyclization of β-(2-pyridyl)propionitriles and γ-(2-pyridyl)butyronitriles, respectively. The reductions must be carried out under conditions such that the pyridine ring is saturated before the nitrile function is reduced, if cyclization is to occur. If the nitrile group is first reduced to the amine, further hydrogenation will result only in the diamine derived by saturation of the pyridine ring; hydrogenation of 2-phenyl-4-(2'-pyridyl)-n-butylamine gave only 2-phenyl-4-(2'-piperidyl)-n-butylamine. Indolizidine (XXII) was prepared in 43% yield, after extraction and distillation, by hydrogenation of 13.2 gm β-(2-pyridyl)propionitrile (XXI) in 50 ml water, 50 ml ethanol, and 16.2 ml 12 N hydrochloric acid over 100 mg platinum oxide. Hydrogen absorption was complete in 8 hours (Boekelheide et al., 1953).

(XXI)   (XXII)
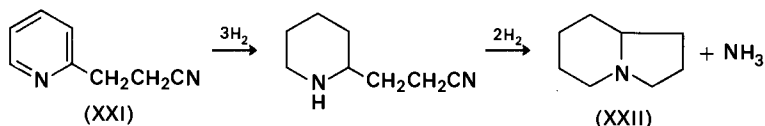
Hydrogenation of γ-carbethoxy-γ-(2-pyridyl)butyronitrile (XXIII) over platinum oxide in ethanol–hydrochloric acid gave a mixture of 1-carbethoxy-quinolizidine (XXIV) and 3-(2'-piperidyl)-2-piperidone (XXV), each in about 30% yield. The quinolizidine is assumed to arise by reduction of the pyridine ring prior to reduction of the nitrile function, whereas XXV is assumed to arise by the reverse sequence (Boekelheide et al., 1953).

(XXIII)   (XXIV)   (XXV)
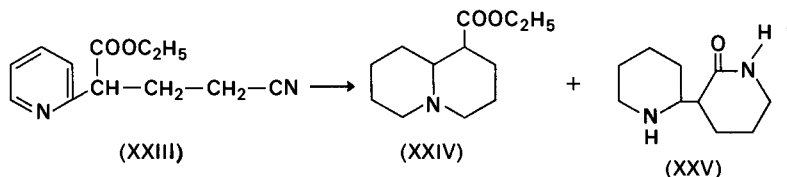
A synthesis of thymine (XXVII) involved reductive cyclization of the aminonitrile, methylcyanacetylurea (XXVI). A solution of XXVI in 30 times its weight of water was shaken over platinum black at 70°C under 1 atm of hydrogen. Heating was discontinued after absorption of one half an equivalent and the reduction interrupted after absorption of one equivalent of hydrogen. Thymine was obtained in high yield (unspecified) (Bergmann and Johnson, 1933) Uracil has been obtained similarly by reductive cyclization of cyanacetylurea over nickel (Rupe *et al.*, 1925).

$$NH_2CNHC-CHCN + H_2 \longrightarrow$$

(XXVI)   (XXVII)
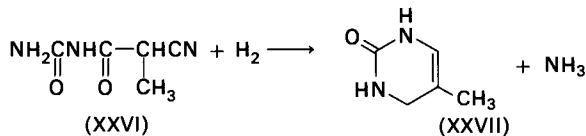
C. DINITRILES

Hydrogenation of aliphatic dinitriles in neutral media may give either cyclic amines or polymers depending on the length of the chain. Glutaronitriles are converted to piperidines and succinonitriles to pyrrolidines (Bergel *et al.*, 1948), whereas adiponitrile gives large quantities of polymeric material with little cyclic product regardless of the catalyst (Tanaka, 1957). In acidic media these nitriles may give the corresponding diamines. For instance, radioactive cadaverine was obtained by hydrogenation of 1,3-dicyanopropane in methanol–hydrochloric acid over platinum oxide at 45 psig. The overall yield from 1,3-dibromopropane and potassium cyanide-^{14}C was 70% (Leete, 1958). Adiponitrile was reduced over a platinum oxide–palladium-on-carbon catalyst in ethanol containing a molar excess of concentrated sulfuric acid to afford hexamethylenediamine in high yield. Hydrochloric acid was also used, but the rate was better in sulfuric acid. Good yields of hexamethylenediamine may be obtained also by carrying out the reduction in the presence of a large excess of ammonia (British Patent 490,922), a reduction that, due to the commercial importance of the product, has been studied extensively.

An impressive example of a hydrogenation of a dinitrile to a diamine is the transformation of 2-chloro-3,4-dicyano-5-nitro-6-methylpyridine (XXVIII) to 3,4-bis(aminomethyl)-5-amino-6-methylpyridine (XXIX), which involves in one step the reduction of four functional groups. The reduction carried

(XXVIII)   (XXIX)

out with 2.2 gm XXVIII, 1.5 ml concentrated sulfuric acid, 1.0 gm 10%
palladium-on-carbon, 5 ml water, and 150 ml methanol required 21 hours
at 40 psig and gave 3.0 gm XXIX as the disulfate. If the reduction is carried
out in hydrochloric acid the trihydrochloride salt is formed (British Patent
626,368).

Hydrogenation of dinitriles in aqueous media may give lactams. Reduction
of succinonitrile over ruthenium dioxide in aqueous ammonia at 1200 psig
and 150°C gave 2-pyrrolidinone in 25% yield (Copenhaver and Ney, 1963).

$$NCCH_2CH_2CN \xrightarrow[H_2O]{H_2}$$

Selective Hydrogenation

Under selected conditions or with limited hydrogen, only one nitrile
group may be reduced. For instance, 4-cyanobenzylamine (XXXI) was
obtained in 97% yield by hydrogenation of 1,4-dicyanobenzene (XXX) over
5% palladium-on-alumina in ethanol–ammonia. Without ammonia the
yield was only 55% (Quin, 1959). The substrate was added in portions, a new
portion being added only when hydrogenation of the previous portion was
complete, as indicated by hydrogen absorption. High yields were obtained
also by limiting the hydrogen absorption to two equivalents (Pietrusza
et al., 1962). In an example, 256 gm XXX in 2000 ml methanol was reduced
over 8 gm 5% palladium-on-carbon at 600–300 psig until two equivalents
had been absorbed. The product consisted of about 10 gm unchanged
substrate, 13 gm *p*-xylylenediamine, and 222 gm XXXI.

$$\begin{array}{ccc} \text{CN} & & \text{CN} \\ & +\ 2H_2 \longrightarrow & \\ \text{CN} & & \text{CH}_2\text{NH}_2 \\ \text{(XXX)} & & \text{(XXXI)} \end{array}$$

Hydrogenation of equal weights of adiponitrile, ammonia, and toluene
over palladium-on-silica at 4500 psig and 110°C gave ω-cyanopentylamine
in 92% yield (German Patent 848,654).

$$NC(CH_2)_4CN + 2H_2 \longrightarrow H_2N(CH_2)_5CN$$

Cyanoform (XXXII) was readily and selectively reduced over 10%
palladium-on-carbon in an ether–water–acetic acid solvent. The reduction
ceased spontaneously, affording 3-amino-2-cyanoacrylonitrile (XXXIII)
as the major product accompanied by 3-amino-2-cyanoacrolein (XXXIV)

in yields of up to 50% (Trofimenko, 1963). The author suggested that the unusually facile hydrogenation supports the dicyanoketeneimine structure for cyanoform. No further reduction of XXXIII could be achieved under

$$CH(CN)_3 \rightleftharpoons \overset{NC}{\underset{NC}{>}}C=C=NH \xrightarrow{H_2} \overset{NC}{\underset{NC}{>}}C=CHNH_2 + \overset{NC}{\underset{CHO}{>}}C=CHNH_2$$

(XXXII)   (XXXIII)   (XXXIV)

mild conditions but, under more vigorous conditions, 50 gm XXXIII in 250 ml ethyl acetate absorbed one equivalent of hydrogen at 1000–1500 psig and 77°C. The resulting solution was chromatographed and the pyridine (XXXV) was obtained in 54% yield.

$$2 \overset{NC}{\underset{NC}{>}}C=CHNH_2 \longrightarrow$$

(XXXIII)   (XXXV)   (54%)

D. NITRILES CONTAINING CARBONYL FUNCTIONS

Amines interact with aldehydes, ketones, amides, and esters and it is to be expected that hydrogenation of a nitrile containing a carbonyl function may also involve that function, particularly if the interaction leads to five- or six-membered rings. Formation of rings provides in itself a way of preventing interaction of the primary amine with intermediate imine, and good yields of cyclic products may frequently be obtained in neutral solution with little or no secondary amine derived by intermolecular condensation. Some coupled product, N-(o-carbomethoxybenzyl)phthalimidine (14%), was formed in hydrogenation of methyl o-cyanobenzoate in ethyl acetate–alcohol–water; the major product was phthalimidine. The percentage of coupled product increased to 28% when the reduction was carried out rapidly, as by using either a very active catalyst or a high catalyst loading (Velluz and Amiard, 1946). The size of the ring formed may also determine, at least in part, the course of the hydrogenation. For instance, hydrogenation

$$\begin{array}{c} CH_3 \\ | \\ C=O \\ | \\ C-(CH_2CH_2CN)_2 \\ | \\ CH_3 \end{array} \longrightarrow$$
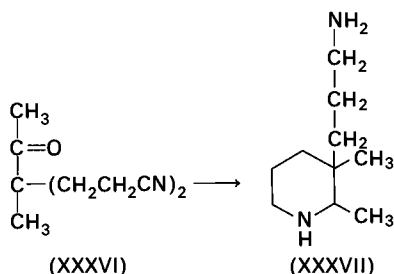
(XXXVI)   (XXXVII)

of γ-aceto-γ-methylpimelonitrile (XXXVI) afforded the piperidine (XXXVII), derived by interaction of the carbonyl function with an amine, rather than the azacyclooctane derived by interaction of the nitrile functions (Japanese Patent 25,047/64).

Whether or not cyclization occurs may depend on the reaction conditions and on details of the substrate structure. The cyano ketone, 2-(β-cyanoethyl)-2-phenylcyclohexanone (XXXVIII), on hydrogenation over platinum oxide in absolute ethanol was converted to 10-phenyldecahydroquinoline (XXXIX),

(XXXVIII)   (XXXIX)
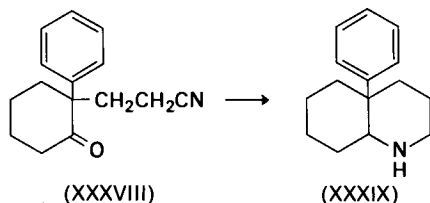
obtained in 40% yield (Boekelheide, 1947). On the other hand, hydrogenation of the lower homolog (XL) over platinum oxide in the presence of ammonia led to a mixture of the amino alcohol (XLI) and a dimer. Hydrogenation of 5 gm XL in ammoniacal alcohol over platinum oxide afforded 0.62 gm XLI and 2.3 gm of a dimer to which structure XLII was tentatively assigned (Boekelheide and Schilling, 1950). One might have expected that hydrogenation of XL in the presence of ammonia would have given a diamine instead of the amino alcohol. The authors noted that, although XL showed a carbonyl peak in its infrared absorption spectra, it did not give the usual carbonyl reactions.

(XL)   (XLI)   (XLII)
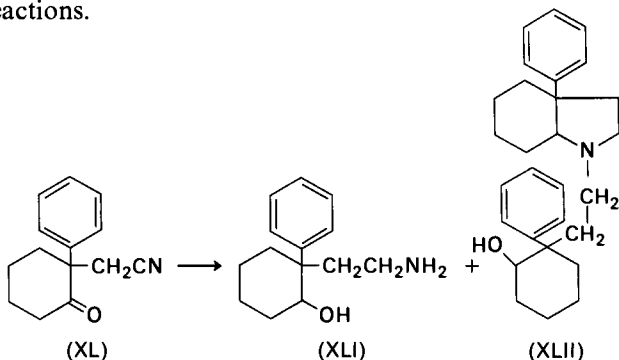
Hydrogenation of o-cyanoacetophenone over palladium in methanol–hydrobromic acid gave 3-methylphthalimidine (Helberger and von Rebay, 1939) in a reduction involving also a hydrolytic step.
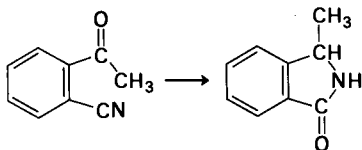
A facile synthesis of hexahydrojulolidine (XLVI) has as the key step the reductive cyclization of cyclohexanone-2,6-dipropionitrile (XLIII). This reduction was the first example of a reductive cyclization of a keto dinitrile to a bicyclic amine. The authors anticipated that the reductive cyclization would proceed stepwise with the formation of XLIV. Hydrogen addition to XLIV was expected to occur from the less hindered side of the molecule to produce the all-*cis* isomer (XLV). This anticipation was fulfilled and, when the hydrogenation was carried out over palladium, XLVI was obtained in 80% yield (Mandell *et al.*, 1963). The hydrogenation was carried out with 3.0 gm cyclohexanone-2,6-dipropionitrile, 25 ml acetic acid, and 1.0 gm palladium-on-carbon at 60 psig. In 20 hours nearly the theoretical amount of hydrogen had been absorbed and the reduction was stopped. This reductive cyclization was applied to homologs of XLIII but the reaction did not proceed so smoothly.

(XLIII)   (XLIV)   (XLV)   (XLVI)
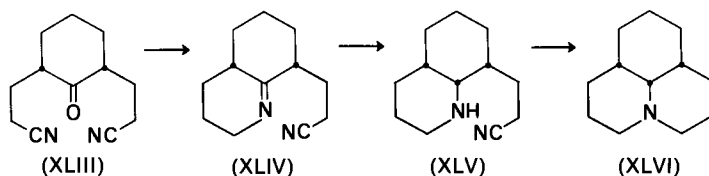
Catalytic hydrogenation of the 3-cyanomethyloxindole (XLVII) led to the pyrrolidone (XLVIII). The aminoethyl group, produced by reduction of the cyano function, ruptured the oxindole ring through interaction with the oxindole carbonyl function. Hydrogenation of XLVII was carried out over platinum oxide in acetic acid–ethanol at atmospheric pressure (Wenkert *et al.*, 1958).

(XLVII)   (XLVIII)
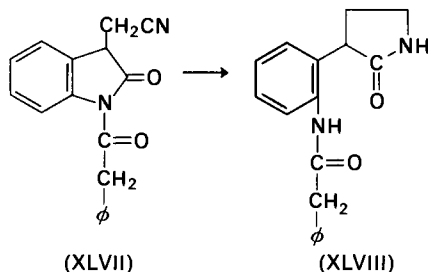
Hydrogenation of γ-cyano esters provided a route to certain azabicyclic compounds. For instance, a mixture of 13.3 gm of the cyano ester (XLIX), 180 ml ethanol, and 20 ml acetic acid was hydrogenated over 0.4 gm platinum

(XLIX)   (L)
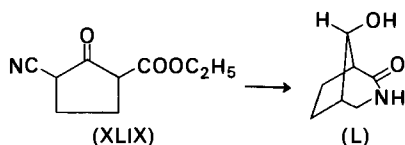
oxide at 1000 psig and 80°C. After filtration, concentration, extraction, and distillation, the bicyclic amide (L) was obtained in 41% yield. A variety of other hydrogenation conditions was explored, but the above procedure, which could be applied to crude undistilled XLIX, proved to be the most reproducible and satisfactory (House et al., 1962).

Hydroxy amides may be obtained by reductive cyclization of γ-cyano-γ-hydroxy esters. For instance, the cyanohydrin of 2-carbethoxymethyl-2-phenylcyclohexanone (LI) on reduction over platinum oxide in ethanol was converted to LII (Boekelheide and Schilling, 1950).
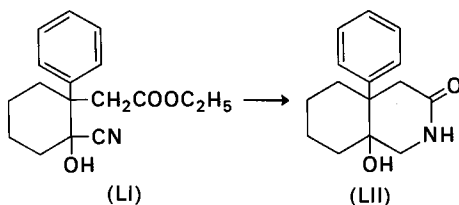
Hydrogenation of β-cyano esters may lead to pyrrolidones, as illustrated by the conversion of LIII to 4-phenyl-3-isonitroso-2-pyrrolidone (LIV) through hydrogenation over platinum oxide in glacial acetic acid. By use of acetic anhydride solvent in the reduction, the 1-acetyl derivative of LIV is obtained. These reductions are particularly interesting in that the isonitroso function is unchanged. Hydrogenation in ethanol of the corresponding amide proceeds similarly with preferential hydrogenation of the nitrile function, but cyclization does not occur and β-phenyl-β-(aminomethyl)-pyruvamide is obtained in 65% yield (Stanek and Urban, 1950).
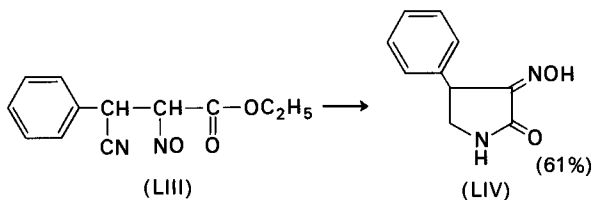
E. NITRO NITRILES

A nitro group is usually hydrogenated in preference to a nitrile group (Snyder et al., 1958; Walker, 1965; Hester, 1964; Clinton and Laskowski, 1952; Bruce and Perez-Medina, 1947), especially if the nitro group is aromatic. (Hydrogenations of this type are discussed in Chapter 11 on hydrogenation of nitro compounds.) The converse preference is rarely seen but can occur. An example is the selective reduction of the nitrile in 4-nitro-4-methyl-valeronitrile (LV), a compound in which the nitro group is both aliphatic and tertiary, two features that render the function unusually resistant to

reduction. Hydrogenation of one mole of LV in 700 ml acetic acid over 2 gm 5% palladium-on-carbon at 14°C and 1500 psig afforded 4-nitro-4-methylpentylamine (LVI) in 64% yield (Young, 1958). Bis(nitroalkyl)-amines are favored by higher temperatures. Subnormal temperatures have been rarely used as a method of controlling secondary amine formation, and the technique appears worthy of further investigation.

$$
\underset{\substack{| \\ NO_2 \\ (LV)}}{CH_3-\overset{\overset{\displaystyle CH_3}{|}}{C}-CH_2CH_2CN} + 2H_2 \longrightarrow \underset{\substack{| \\ NO_2 \\ (LVI)}}{CH_3-\overset{\overset{\displaystyle CH_3}{|}}{C}-CH_2CH_2CH_2NH_2}
$$
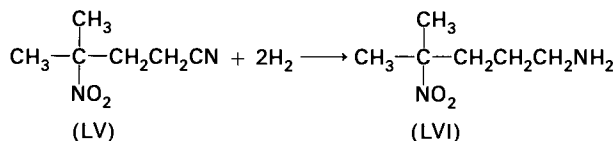
F. OXIMINO NITRILES

Both oximes and nitriles may be reduced to amines, but their simultaneous reduction to a diamine has at times proved to be difficult. A case in point is the hydrogenation of 5-cyano-2-oximinovaleric acid to DL-lysine (Ferris et al., 1960a).

$$
\underset{}{NC(CH_2)_3\overset{\overset{\displaystyle HON}{\|}}{C}-COOH} \longrightarrow \underset{}{NH_2(CH_2)_4\overset{\overset{\displaystyle NH_2}{|}}{C}H-COOH}
$$
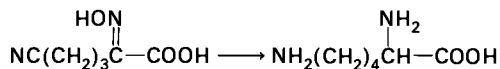
A number of catalyst systems, including platinum and palladium-on-charcoal in ethanol–hydrochloric acid, and Raney nickel and platinum metal in ethanol–ammonia, were tried without success. In many reductions the theoretical amount of hydrogen was absorbed but in no case was lysine obtained. The products were probably secondary amines. The technique of preventing secondary amine formation by carrying out the hydrogenation in acetic anhydride was not applicable in this case, as the solvent interacted with the substrate to produce glutaronitrile and carbon dioxide. Moderately successful reductions were achieved finally by carrying out the hydrogenations over platinum oxide in acetic acid. A solution of 7.8 gm (0.10 mole) 5-cyano-2-oximinovaleric acid in 100 ml glacial acetic acid was shaken with 0·6 gm platinum oxide at 50 psig. Theoretical hydrogen was absorbed in 8 hours and DL-lysine, isolated as the monohydrochloride, was obtained in 43% yield.

The reduction could be carried out successfully in acetic anhydride if an ester instead of the free acid were used. A solution of ethyl 5-cyano-2-oximinovalerate (0.20 mole) in 200 ml acetic anhydride was shaken over 3.0 gm platinum oxide for 8 hours at 50 psig. Hydrolysis of the product gave lysine, isolated as the monohydrochloride, in 57% yield. In a later paper (Ferris et al., 1960b), a much better way of reducing the ester was described. Excellent yields of lysine were obtained by carrying out the hydrogenation

over a Raney nickel catalyst in acetic anhydride solvent in the presence of a basic cocatalyst, such as sodium acetate, sodium hydroxide, potassium hydroxide, or benzyltrimethylammonium hydroxide. Very poor yields of lysine were obtained when no basic cocatalyst was used. (Examples of the selective hydrogenation of the nitrile function in oximino nitriles are given on page 222.)

G. OLEFINIC NITRILES

Olefins are hydrogenated rapidly and easily and the selective hydrogenation of the carbon–carbon double bond in an unsaturated nitrile usually presents no problem. A number of such examples are given in Chapter 5. Small amounts of nitrile may also be reduced in these hydrogenations, but the amount of nitrile reduced may usually be kept to low levels by attention to the operating conditions or by limiting the hydrogen absorbed.

Selective hydrogenations in the reverse sense are rare. An interesting example is the selective hydrogenation of the nitrile function in the un-saturated bromocyanamide (LVII) derived from the alkaloid virosecurinine by the action of cyanogen bromide (Nakano et al., 1963). The reduction was carried out over 5% palladium-on-carbon in ethanol and was stopped after the rapid absorption of two equivalents of hydrogen to afford LVIII. The allylic bromide might have been expected to be removed easily, but the selective reduction of the nitrile is surprising, especially in view of the facile saturation of the less hindered double bond in the amide derived by hydrolysis of the imine.

(LVII)   (LVIII)
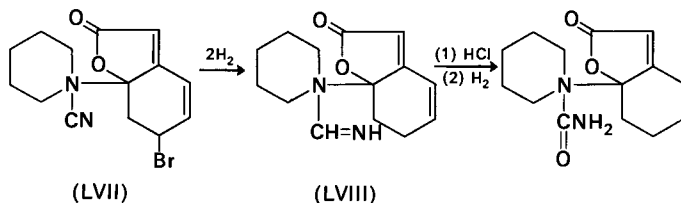
Hydrogenation of LVII proceeded quite differently than that of LIX derived from tetrahydroberberine by the action of cyanogen bromide. Hydrogenation of LIX in acetic acid over 10% palladium-on-carbon re-constituted tetrahydroberberine (Sallay and Ayers, 1963).

(LIX)
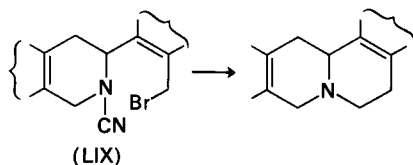
REFERENCES

Bergel, F., Morrison, A. L., and Rinderknecht, H., U.S. Patent 2,446,803, Aug. 10, 1948.

Bergmann, W., and Johnson, T. B., *J. Am. Chem. Soc.* **55**, 1733 (1933).

Boekelheide, V., *J. Am. Chem. Soc.* **69**, 790 (1947).

Boekelheide, V., and Schilling, W. M., *J. Am. Chem. Soc.* **72**, 712 (1950).

Boekelheide, V., Linn, W. J., O'Grady, P., and Lamborg, M., *J. Am. Chem. Soc.* **75**, 3243 (1953).

Bruce, W. F., and Perez-Medina, L. A., *J. Am. Chem. Soc.* **69**, 2571 (1947).

Buck, J. S., *J. Am. Chem. Soc.* **55**, 2593 (1933).

Carothers, W. H., and Jones, G. A., *J. Am. Chem. Soc.* **47**, 3051 (1925).

Chiavarelli, S., and Marini-Bettolo, G. B., *Gazz. Chim. Ital.* **86**, 515 (1956).

Clinton, R. O., and Laskowski, S. C., *J. Am. Chem. Soc.* **74**, 2226 (1952).

Cope, A. C., Nace, H. R., and Estes, L. L., Jr., *J. Am. Chem. Soc.* **72**, 1123 (1950).

Copenhaver, J. W., and Ney, W. O., U.S. Patent 3,095,423, June 25, 1963.

Ferris, A. F., Johnson, G. S., Gould, F. E., and Latourette, H. K., *J. Org. Chem.* **25**, 492 (1960a).

Ferris, A. F., Johnson, G. S., Gould, F. E., and Stange, H., *J. Org. Chem.* **25**, 1302 (1960b).

Freifelder, M., *J. Am. Chem. Soc.* **82**, 2386 (1960).

Freifelder, M., and Hasbrouck, R. B., *J. Am. Chem. Soc.* **82**, 696 (1960).

Freifelder, M., and Ng, Y. H., *J. Pharm. Sci.* **54**, 1204 (1965).

Giner-Sorolla, A., and Bendich, A., *J. Am. Chem. Soc.* **80**, 3932 (1958).

Griffin, G. W., Basinski, J. E., and Peterson, L. I., *J. Am. Chem. Soc.* **84**, 1012 (1962).

Gutsche, C. D., *J. Am. Chem. Soc.* **71**, 3513 (1949).

Hartung, W. H., *J. Am. Chem. Soc.* **50**, 3370 (1928).

Hawkins, W. L., and Biggs, B. S., *J. Am. Chem. Soc.* **71**, 2530 (1949).

Helberger, J. H., and von Rebay, A., *Ann. Chem. Liebigs* **539**, 187 (1939).

Hester, J. B., Jr., *J. Org. Chem.* **29**, 1158 (1964).

House, H. O., Grubbs, E. J., and Gannon, W. F., *J. Am. Chem. Soc.* **82**, 4099 (1960).

House, H. O., Wickham, P. P., and Müller, H. C., *J. Am. Chem. Soc.* **84**, 3139 (1962).

Huber, W., *J. Am. Chem. Soc.* **66**, 876 (1944).

Juday, R., and Adkins, H., *J. Am. Chem. Soc.* **77**, 4559 (1955).

Kindler, K., and Hesse, F., *Arch. Pharm.* **271**, 439 (1933).

Kindler, K., Peschke, W., and Dehn, W., *Ann. Chem. Liebigs* **485**, 113 (1931).

Kindler, K., Shrader, K., and Middelhoff, B., *Arch. Pharm.* **283**, 184 (1950).

Leete, E., *J. Am. Chem. Soc.* **80**, 4393 (1958).

McBee, E. T., and Wiseman, P. A., U.S. Patent 2,515,246, July 18, 1950.

Mandell, L., Piper, J. U., and Singh, K. P., *J. Org. Chem.* **28**, 3440 (1963).

Mignonac, G., *Compt. Rend.* **171**, 1148 (1920).

Miyatake, K., and Tsunoo, M., *Yakugaku Zasshi* **72**, 630 (1952).

Musso, H., and Figge, K., *Chem. Ber.* **95**, 1844 (1962).

Nakano, T., Yang, T. H., and Terao, S., *Tetrahedron* **19**, 609 (1963).

Odo, K., Ichikawa, E., Shirai, K., and Sugino, K., *J. Org. Chem.* **22**, 1715 (1957).

Overberger, C. G., and Mulvaney, J. E., *J. Am. Chem. Soc.* **81**, 4697 (1959).

Pietrusza, E. W., Brown, R. E., and Mueller, M. B., U.S. Patent 3,050,544, Aug. 21, 1962.

Plieninger, H., and Werst, G., *Chem. Ber.* **88**, 1956 (1955).

Quin, D. C., British Patent 814,631, June 10, 1959.

Reihlen, H., von Hessling, G., Hühn, W., and Weinbrenner, E., *Ann. Chem. Liebigs* **493**, 20 (1932).

Ringold, H. J., *J. Am. Chem. Soc.* **82**, 961 (1960).

Rogers, A. O., U.S. Patent 3,078,274, Feb. 19, 1963.

Rosenmund, K. W., and Pfannkuch, E., *Chem. Ber.* **56B**, 2258 (1923).

Rupe, H., Metzger, A., and Vogler, H., *Helv. Chim. Acta* **8**, 848 (1925).

Rylander, P. N., and Kaplan, J., Paper presented at the *Am. Chem. Soc. Meeting, New York, Sept., 1960.*

Rylander, P. N., and Steele, D. R., *Engelhard Ind. Tech. Bull.* **5**, 113 (1965).

Saito, N., Tanaka, C., and Takatani, S., *Yakugaku Zasshi* **76**, 341 (1956).

Sallay, I., and Ayers, R. H., *Tetrahedron* **19**, 1397 (1963).

Snyder, H. R., Merica, E. P., Force, C. G., and White, E. G., *J. Am. Chem. Soc.* **80**, 4622 (1958).

Stanek, J., and Urban, J., *Collection Czech. Chem. Commun.* **15**, 397 (1950).

Stegemeyer, L. A., U.S. Patent 2,408,959, Oct. 8, 1946.

Strack, E., and Schwaneberg, H., *Chem. Ber.* **65B**, 710 (1932).

Tanaka, W., Unpublished observations, Engelhard Ind., 1957.

Tchoubar, B., *Bull. Soc. Chim. France* p. 160 (1949).

Trofimenko, S., *J. Org. Chem.* **28**, 2755 (1963).

van Tamelen, E. E., and Smissman, E. E., *J. Am. Chem. Soc.* **75**, 2031 (1953).

Velluz, L., and Amiard, G., *Bull. Soc. Chim. France* p. 690 (1946).

Vinogradova, A. I., and Arkhangel'skaya, V. N., *J. Gen. Chem. USSR (English Transl.)* **16**, 301 (1946).

von Braun, J., Blessing, G., and Zobel, F., *Chem. Ber.* **56B**, 1988 (1923).

Walker, G. N., *J. Med. Chem.* **8**, 583 (1965).

Weijlard, J., Swanezy, E. F., and Tashjian, E., *J. Am. Chem. Soc.* **71**, 1889 (1949).

Wenkert, E., Bernstein, B. S., and Udelhofen, J. H., *J. Am. Chem. Soc.* **80**, 4899 (1958).

Winans, C. F., and Adkins, H., *J. Am. Chem. Soc.* **54**, 306 (1932).

Young, V. V., U.S. Patent 2,864,863, Dec. 16, 1958.

13

Hydrogenation of Acids, Esters, and Anhydrides

I. ACIDS

Acids are not reduced easily over platinum metal catalysts. Hydrogenation at ambient temperatures, if it occurs at all, goes very slowly or incompletely. Under vigorous conditions, good yields of alcohols have been obtained by hydrogenation of carboxylic acids over ruthenium, which seems to be the best of the platinum metals for this purpose. Ruthenium catalysts smoothly reduce carboxylic acids to the corresponding alcohols at 9000–10,500 psig and 130–255°C; either ruthenium dioxide or ruthenium-on-carbon catalyst is effective. The chief side-reaction is hydrogenolysis of the alcohol, but the yield of alcohol nonetheless is often good, ranging up to 88%. Hydroxy acids and dicarboxylic acids are reduced to the corresponding glycol (Carnahan et al., 1955; Ford, 1952). Perfluorooctanoic acid is reduced to the perfluoro alcohol over 5% ruthenium-on-carbon in ethyl ether at 175°C and 5000 psig (Schreyer, 1958).

Aldehydes may result from hydrogenation of carboxylic acids, as exemplified by the conversion of D-gluconic acid to D-glucose over platinum oxide (Glattfeld and Shaver, 1927). This hydrogenation was carried out in neutral or slightly acidic media, since it was shown earlier that glucose was not reduced over platinum black under these conditions (Cake, 1922). The yield was only 14–28% and the catalyst loading was high. In these reductions, the platinum oxide catalyst was modified by the incorporation of 0.2 gm ferrous sulfate per 3 gm platinum.

Carboxylic acids are reduced very slowly over platinum oxide in the presence of perchloric acid, and this may prove a nuisance if the acid is used as a solvent. If the substrate is itself slowly reduced, the concomitant reduction of the solvent can lead to serious errors in the absorption measurements (Chanley and Mezzetti, 1964). Acetic acid is rapidly reduced over rhodium catalysts at room temperature and pressure, but the reduction stops abruptly after a very small conversion. Nonetheless the reduction is

sufficient to introduce appreciable error in absorption measurements. In hydrogenation of nitriles in acetic acid over rhodium catalysts, invariably something more than theoretical hydrogen was absorbed due to reduction of acetic acid itself. Ethanol and ethyl acetate were identified in the reduction mixture (Kaplan, 1960).

Hydrogenation in alcohol solvent of compounds containing other functions in addition to a carboxyl group is apt to give ester derivatives instead of the free acid. In reduction of benzoic acid to hexahydrobenzoic acid and of cinnamic acid in methanol or 95% ethanol, the formation of esters was shown to be caused by traces of hydrochloric acid produced by hydrogenolysis of chloride still bound to the catalyst. When platinum oxide or palladium oxide catalysts that were completely chloride-free were used, no esterification occurred (Kindler and Helling, 1957).

II. ESTERS

Esters, with a few exceptions, are reduced with difficulty and survive most catalytic hydrogenations. Esters, like acids, frequently make excellent solvents because of their inertness toward hydrogenation. Reduction is accomplished readily only in those molecules whose special structural features render the ester exceptionally prone to hydrogenolysis, or in those molecules, that permit and favor an intermediate alkene. The products of ester hydrogenation may be alcohols, acids, ethers, or hydrocarbons, depending on the mode of attack, which seems to be determined largely by the substrate itself. Presumably a different platinum metal catalyst would alter the course of reduction somewhat, but examples of ester hydrogenation over platinum metals are so few that no conclusion regarding the effect of metal can be reached.

A. HYDROGENOLYSIS TO ACIDS

Hydrogenolysis of esters to acids,

$$R-O-\underset{\substack{\|\\O}}{C}-R' + H_2 \longrightarrow RH + HO-\underset{\substack{\|\\O}}{C}-R'$$
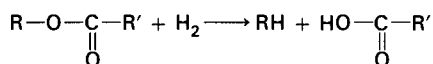
occurs readily when some structural feature of R weakens the R—O bond, as exemplified by the hydrogenolysis of benzyl or allyl esters. Considerable hydrogenolysis may also occur when R is aryl or vinyl. (These and related reductions are discussed in detail in the section on hydrogenolysis.) Except for compounds in the above groups, hydrogenolysis of esters to acids under mild conditions is relatively rare. An unusual example was observed in

the catalytic reduction of ω-acetoxy-2-acetobenzofuran over platinum oxide. The major products were acetic acid and 2-acetobenzofuran:
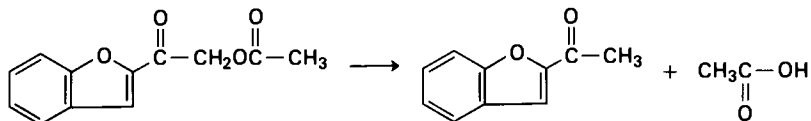
This cleavage reaction is not general. Under similar conditions a closely related compound, phenacyl acetate, gave a good yield of 1-phenyl-2-acetoxy-ethanol (Shriner and Anderson, 1939):
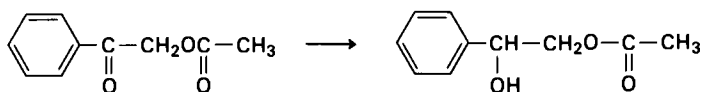
Certain esters of 4-deoxypyridoxine undergo a facile hydrogenolysis over a mixture of platinum oxide and palladium-on-carbon. Reduction of I resulted in cleavage of both the ester and benzyl function to yield II.
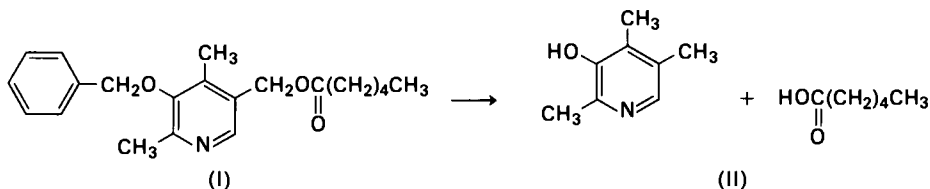
The 3,5-diesters (III) undergo hydrogenolysis only at the 5-position to give the 3-ester of 2,4,5,-trimethyl-3-pyridinol (IV) (Sakuragi, 1958).
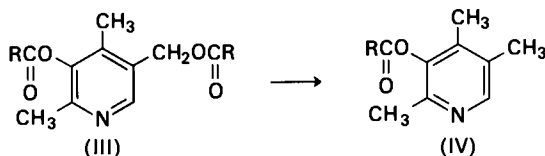
Acids may also be formed in ester hydrogenolysis, if the structural features are such as to promote formation of an actual or incipient alkene. For instance, tertiary alcohols and esters are reduced at room temperature and pressure over platinum oxide in trifluoroacetic acid solvent, probably via an alkene intermediate. The authors suggest that this reduction may have some value in accomplishing the selective removal of a tertiary oxygen (Peterson and Casey, 1964).

Certain bromo esters and bromo lactones undergo a facile hydrogenolysis. Dehydrobromination of the bromo lactone (V), over palladium-on-carbon in ethanol containing one equivalent of potassium acetate, was accompanied by hydrogenolysis of the lactone. The product was a mixture of the debromo

lactone (VI) and the acid (VII). Since the lactone (VI) was stable toward hydrogenolysis, the acid must have arisen during displacement of the bromine (Denton *et al.*, 1964).
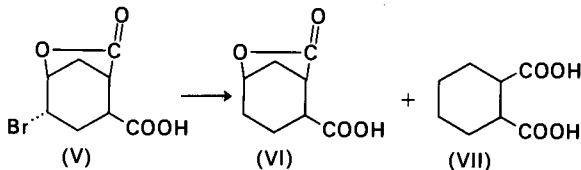
The authors suggested that VII was formed through hydrogenation of an intermediate olefin derived by elimination in an organometallic derivative (Campbell and Kemball, 1963):
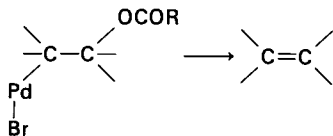
A similar bromo lactone (VIII) was debrominated without hydrogenolysis of the lactone ring, presumably because the requisite bicycloheptene intermediate is strained:
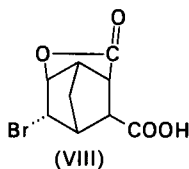
A facile hydrogenolysis of an acetoxy group was observed in reduction of a 17α-bromo-3β,16β-diacetoxy-5α-pregnan-20-one over 5% palladium-on-carbon in methanol (Levine and Wall, 1959):
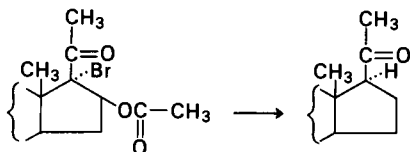
In contrast, a bromohydrin in the Δ^5-pregnene series, with the same D ring structure as above, on reduction over 5% palladium-on-carbon in methanol containing ammonium acetate, gave the 16β-hydroxy-20-ketone:
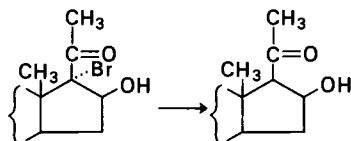
Ammonium acetate was used in this reaction to prevent reduction of the Δ^5 double bond (Löken *et al.*, 1956).

Temperature

Ester hydrogenolysis may be greatly facilitated by elevated temperatures. Acetic acid esters are smoothly reduced at 300°C and atmospheric pressure over platinum or palladium catalysts; at 250°C there is but little reduction. The products of the reduction are acetic acid and alkanes (Shuikin *et al.*, 1961). This paper also discusses base metal catalysts for reduction of esters.

B. HYDROGENOLYSIS TO A HYDROCARBON

Hydrogenolysis and reduction of the acyl portion of an ester over platinum metals have been observed, but the reaction is by no means common:

$$R-O-\underset{\underset{O}{\|}}{C}-R' \longrightarrow R-OH(\text{or } R-H) + R'CH_3$$
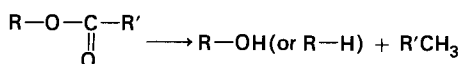
Reduction of ethyl 5,6-benzocoumarin-3-carboxylate in ethanol over 5% rhodium-on-alumina at high catalyst loading levels reduced both aromatic rings under mild conditions, and at the same time caused hydrogenolysis of the lactone (but not the ester) (Liska and Salerni, 1960).

(67%)
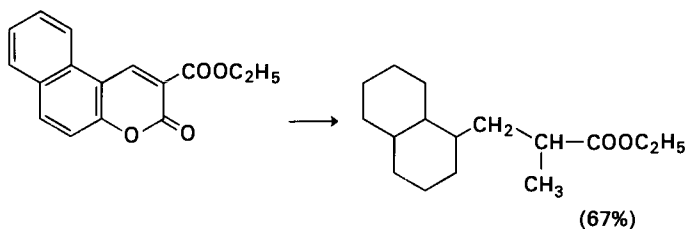
Esters of 2- or 4-pyridinol and 2- or 4-quinolinol aromatic acids are easily reduced over palladium to hydrocarbon derivatives of the aromatic acid. Apparently the weak ester linkage is cleaved by hydrogen to give the original hydroxy compound and the aromatic aldehyde, which is further reduced:
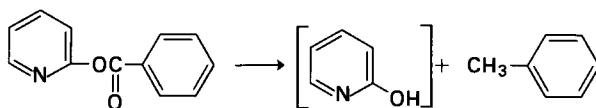
This reduction is exceptionally facile. For instance, under the same hydrogenation conditions, benzoyl chloride absorbed only 10% of the theoretical hydrogen required to give toluene. This interesting reduction of these

esters appears to have been studied no further. It seems to offer possibilities for a general method for reduction of carboxylic acids under mild conditions. Platinum oxide was ineffective in these reductions (Cavallito and Haskell, 1944).

C. FORMATION OF ETHERS

The reduction of esters to ethers,

$$R-O-\underset{\underset{O}{\parallel}}{C}-R' + 2H_2 \longrightarrow R-O-CH_2R' + H_2O$$
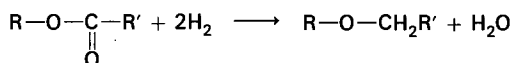
is competitive with hydrogenolysis to acids, and one might assume that ether formation would be limited to those substrates where the structure of R does not favor formation of acids, and where R' is not aromatic, which would favor further hydrogenolysis of the ether if it were formed.

Reductions of esters to ethers are apparently best carried out in the presence of acid. Hydrogenation of dihydrolanosteryl and dihydroagnosteryl acetates over platinum oxide in acetic acid containing perchloric acid led to a mixture of saturated products, including the 3β-ethoxy derivatives formed by reduction of the ester function. The reduction was slow and the catalyst loading high. The uptake of hydrogen was greatly in excess of that calculated, due to reduction of the acetic acid solvent in the presence of perchloric acid (Chanley and Mezzetti, 1964).

The reduction to ethers is sensitive to subtle structural features. δ-Lactones have been reduced in high yield over platinum oxide in acetic acid. For instance, an ether was formed in 80–90% yield by reduction of 10-methyl-1-oxa-2-oxodecalin,
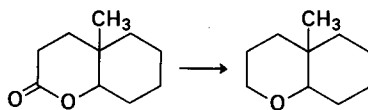
and 4-oxa-3-oxo-5α-cholestane afforded a 92% yield of 4-oxa-5α-cholestane. The addition of precisely regulated amounts of 70% perchloric acid to the acetic acid greatly accelerated the reduction; with 20 mg of the steroid, 18 mg platinum oxide, 5 ml acetic acid, and 0.030 ml perchloric acid, the reduction was complete in 15 minutes. Without perchloric acid it required 9 hours. Several other δ-lactones were reduced with similar results, but the facile reduction observed with δ-lactones apparently does not extend to γ- or ε-lactones. Under the above conditions, the γ-lactones, γ-butyrolactone, γ-valerolactone, cis-1-oxa-2-oxohydrindane, and trans-1-oxa-2-oxohydrindane, and the ε-lactones, 3a-oxa-3-oxo-A-homo-5α-cholestane and 7a-oxa-7-oxo-B-homo-5α-cholestane, were unchanged in 12 hours (Edward and Ferland, 1964).

D. HYDROGENOLYSIS TO THE ALCOHOL

Hydrogenolysis of an ester to alcohols,

$$R—O—\underset{\underset{O}{\|}}{C}—R' + 2H_2 \longrightarrow ROH + R'CH_2OH$$
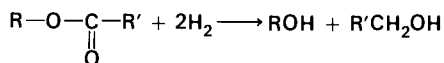
is not often observed over platinum metals. This reduction is usually carried out at high temperatures and pressures over copper-chromium oxide catalysts (Adkins, 1954).

An example with a platinum metal catalyst is found in the hydrogenation of the ethyl ester of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid. Reduction of this compound over 5% rhodium-on-alumina in ethanol at 50°C and 750 psig gave 3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline. This reduction is also unusual in that the ester was reduced in preference to the aromatic ring:
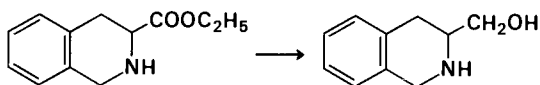
Hydrogenation of the free acid did result in ring saturation, with formation of cis-3-carboxydecahydroisoquinoline (Rapala et al., 1957).

III. ANHYDRIDES

Anhydrides survive most catalytic hydrogenations unchanged but, if the catalyst loading is high or the reduction prolonged or vigorous, this function too will be reduced to products that depend in large measure on the structure of the substrate. Aliphatic anhydrides undergo a slow hydrogenolysis over palladium and platinum catalysts (Musso and Figge, 1962), which can be a source of error in determining hydrogen absorption of a substrate dissolved, for instance, in the often used acetic acid–acetic anhydride solvent mixture.

Hydrogenation of anhydrides may lead to hemiacylals, to esters, or to a hydrocarbon and an acid. The major product depends on the substrate, and on the conditions and length of the reduction. Catalytic hydrogenation of phthalic anhydride over platinum sponge in acetic acid gave first phthalide that was further reduced to hexahydrophthalide, o-toluic acid, and hexahydrotoluic acid. The catalyst was rapidly deactivated, but activity was easily restored by removing hydrogen from the system and shaking the reaction mixture for 1 minute with air (Willstätter and Jaquet, 1918).

Reduction of the aliphatic anhydride (I) over platinum oxide in ethyl acetate at 1 atm gave >90% yield of the hydroxy lactone (II) and <2% of the lactone (III). In acetic acid the anhydride (I) afforded equal amounts

of the lactone (III) and the methyl acid (IV). Under these conditions III was recovered unchanged, showing that it was not a precursor of IV. In all reductions the same carbonyl group was transformed (McCrindle *et al.*, 1961). This work was later extended to other derivatives so that a correlation of products with substrate might be made. However, on completion of the work the authors concluded that they were not justified in trying to rationalize the results without further study (McCrindle *et al.*, 1962).
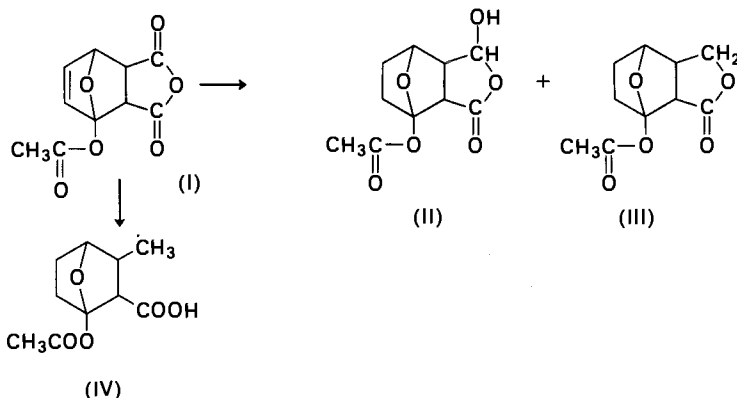
Simple cyclic anhydrides may be converted to lactones, sometimes in excellent yield. Hydrogenation of cyclooct-1-ene-1,2-dicarboxylic anhydride over platinum dioxide in dioxane gave a mixture of the saturated anhydride and lactone (Sicher *et al.*, 1961). High yields of butyrolactone are obtained by hydrogenation of succinic anhydride over a palladium-on-carbon or palladium-on-alumina catalyst in ethyl acetate or dioxane at 800–1200 psig and 50–100°C (Franko-Filipasic *et al.*, 1963). If the reaction is carried out over platinum oxide in ethyl acetate at 1 atm pressure, a mixture of 20% butyric acid and 80% butyrolactone is formed (McCrindle *et al.*, 1962).
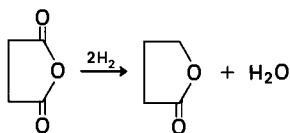
However, the only product that could be isolated from hydrogenation over platinum oxide of the strained anhydride (V) was the methyl acid (VI) (McCrindle *et al.*, 1961).
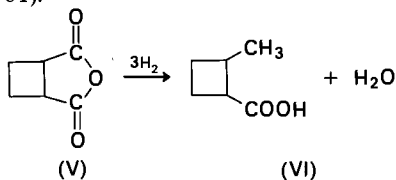
REFERENCES

Adkins, H., *Org. Reactions* **8**, 1 (1954).

Cake, W. E., *J. Am. Chem. Soc.* **44**, 861 (1922).

Campbell, J. S., and Kemball, C., *Trans. Faraday Soc.* **59**, 2583 (1963).

Carnahan, J. E., Ford, T. A., Gresham, W. F., Grisby, W. E., and Hager, G. F., *J. Am. Chem. Soc.* **77**, 3766 (1955).

Cavallito, C. J., and Haskell, T. H., *J. Am. Chem. Soc.* **66**, 1166 (1944).

Chanley, J. D., and Mezzetti, T., *J. Org. Chem.* **29**, 228 (1964).

Denton, D. A., McQuillin, F. J., and Simpson, P. L., *Proc. Chem. Soc.* p. 297 (1964).

Edward, J. T., and Ferland, J. M., *Chem. Ind. (London)* No. 23, 975 (1964).

Ford, T. A., U.S. Patent 2,607,807, Aug. 19, 1952.

Franko-Filipasic, B. R., Kolyer, J. M., and Burks, R. E., Jr., U.S. Patent 3,113,138, Dec. 3, 1963.

Glattfeld, J. W. E., and Shaver, E. H., *J. Am. Chem. Soc.* **49**, 2305 (1927).

Kaplan, J., Unpublished observations, Engelhard Ind., 1960.

Kindler, K., and Helling, H. G., *Chem. Ber.* **90**, 750 (1957).

Levine, S. G., and Wall, M. E., *J. Am. Chem. Soc.* **81**, 2829 (1959).

Liska, K. J., and Salerni, L., *J. Org. Chem.* **25**, 124 (1960).

Löken, B., Kaufmann, S., Rosenkranz, G., and Sondheimer, F., *J. Am. Chem. Soc.* **78**, 1738 (1956).

McCrindle, R., Overton, K. H., and Raphael, R. A., *Proc. Chem. Soc.* p. 313 (1961).

McCrindle, R., Overton, K. H., and Raphael, R. A., *J. Chem. Soc.* p. 4799 (1962).

Musso, H., and Figge, K., *Chem. Ber.* **95**, 1844 (1962).

Peterson, P. E., and Casey, C., *J. Org. Chem.* **29**, 2325 (1964).

Rapala, R. T., Lavagnino, E. R., Shepard, E. R., and Farkas, E., *J. Am. Chem. Soc.* **79**, 3770 (1957).

Sakuragi, T., *J. Org. Chem.* **23**, 129 (1958).

Schreyer, R. C., U.S. Patent 2,862,977, Dec. 2, 1958.

Shriner, R. L., and Anderson, J., *J. Am. Chem. Soc.* **61**, 2705 (1939).

Shuikin, N. I., Bel'skii, I. F., and Shostakovskii, V. M., *Dokl. Akad. Nauk SSSR* **139**, 634 (1961).

Sicher, J., Sipos, F., and Jonas, J., *Collection Czech. Chem. Commun.* **26**, 262 (1961).

Willstätter, R., and Jaquet, D., *Chem. Ber.* **51**, 767 (1918).

14

Hydrogenation of Aldehydes

The preferred catalyst system for hydrogenation of aldehydes depends, among other things, on whether the aldehyde is aliphatic or aromatic, saturated or unsaturated, and on the product desired. Hydrogenation of aldehydes, particularly unsaturated aldehydes, is enormously influenced by the presence of various additives, which may alter the rate and course of reduction as well as protect the catalyst against deactivation. Catalyst promotion is discussed specifically in one section, but is also a recurring theme throughout the chapter.

I. SATURATED ALIPHATIC ALDEHYDES

Aliphatic aldehydes are reduced to the corresponding alcohols over platinum metal catalysts with little danger of overhydrogenation. Platinum has been the most used catalyst, but from limited data it appears that ruthenium may frequently be a more active catalyst. Hydrogenations of aliphatic aldehydes are relatively slow, and elevated temperatures and pressures may be used to advantage. Promoters are frequently used in hydrogenations of saturated aldehydes, mainly to preserve catalyst activity.

A. Catalyst Promotion

Certain metallic salts are known to be promoters for reduction of aldehydes over supported and unsupported palladium, platinum, and ruthenium catalysts. Promotion means here a change in character of the catalyst that may be reflected in an increased rate of hydrogenation, an increased catalyst life, or a change in the products of reduction. (Notable examples of promoters changing the course of reduction are found in the section on hydrogenation of unsaturated aldehydes.)

It has long been known that platinum oxide is quickly deactivated when used in reduction of aldehydes, but when small amounts of certain metallic

salts, such as ferrous chloride, are added the reduction goes rapidly to completion (Carothers and Adams, 1923, 1925; Tuley and Adams, 1925; Adams and Garvey, 1926). The additive was assumed to function by inhibiting reduction of active platinum oxide to an inactive platinum of lower oxidation state. This suggestion stemmed from the experimental observation that platinum catalysts deprived of their oxygen lost activity, but that activity could be readily restored by shaking the reaction mixture with oxygen (Willstätter and Jaquet, 1918), which presumably restored the oxide film. Maxted and Akhtar (1959) examined the effect of various promoters in hydrogenation of valeraldehyde over platinum oxide. Stannous chloride was by far the most effective promoter tested. The addition of only 10^{-5} mole of stannous chloride to 1.1×10^{-3} mole of platinum oxide increased the rate of hydrogenation in ethanol about ten times. The promoting effect of stannous chloride was especially high in ethanol; in ethyl acetate, the rate was increased only about four times. Prereduced platinum black, on the other hand, was poisoned by stannous chloride. The authors attributed the promoting effect of metallic salts in these reductions to their action in preventing autocatalytic reduction of platinum oxide to the metal.

Supported catalysts can also be promoted by certain metal salts. Figure 1 has rate curves for hydrogenation of heptaldehyde over platinum oxide,
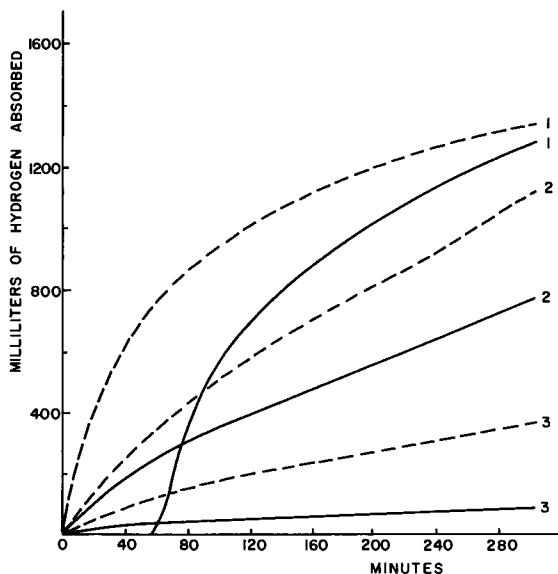
Fig. 1. Effect of stannous chloride on the rate of hydrogenation of heptaldehyde (one mole $H_2 \equiv 1600$ ml at 25°C): (1) 5% ruthenium-on-carbon, 1000 mg, (2) 5% platinum-on-carbon, 1000 mg, and (3) platinum oxide, 59.7 mg. Solvent: 44.5% v/v aqueous ethanol. Solid line = no promoter; broken line = one atom Sn^{++} per atom Ru or Pt.

5% platinum-on-carbon, and 5% ruthenium-on-carbon, unpromoted and promoted by stannous chloride, the most effective salt of many tested (Rylander and Kaplan, 1961). Hydrogenations over both supported and unsupported platinum are appreciably more rapid in the promoted system. Stannous chloride affects hydrogenation over ruthenium catalysts primarily by eliminating the induction period. Catalytic hydrogenations over ruthenium often show induction periods, which usually can be eliminated entirely by prereduction, i.e., by shaking the catalyst and solvent together with hydrogen at room temperature and atmospheric pressure before adding the substrate. When a freshly prepared ruthenium catalyst, which had no induction period, was used in these experiments, stannous ion in 1 : 1 molar ratio had no effect on the rate at all. Larger amounts of stannous ion tended to poison the catalyst.

Ruthenium catalyst may be promoted by other platinum metals. For instance, a 4% ruthenium, 1% palladium-on-carbon catalyst was shown to be three to four times more active than 5% ruthenium-on-carbon catalyst for hydrogenation of heptaldehyde in water. The activity of these promoted ruthenium catalysts depends on the support and also on the substrate. Calcium carbonate was shown to be a more effective support than carbon for hydrogenation of heptaldehyde, cyclohexanone, and levulose, but the reverse was true for hydrogenation of acetone and methyl ethyl ketone (Koch, 1962).

B. Oxygen Reactivation

The overall activity of platinum-on-carbon and ruthenium-on-carbon (Rylander and Kaplan, 1961) as well as platinum oxide (Carothers and Adams, 1923, 1925) can be improved by periodic shaking with oxygen, when these catalysts are used for hydrogenation of an aldehyde (Fig. 2). The beneficial effect of oxygen on ruthenium catalysts is surprising, inasmuch as ruthenium catalysts, when used at atmospheric pressure, usually have to be prereduced by shaking with hydrogen, presumably to reduce the ruthenium to a lower valence. The fact that the activity of supported platinum, as well as platinum oxide, is enhanced by periodic shaking with oxygen militates against the idea that the sole function of oxygen in platinum oxide reactivation is restitution of the catalyst to its original physical form (Voorhees and Adams, 1922). Catalyst reactivation by shaking with air might be attributed to flushing out of catalyst poisons, possibly carbon monoxide (Hoffman et al., 1962); periodic or continuous venting is often practiced industrially to remove accumulated poisons. However, this did not seem to be the case here; shaking with nitrogen, instead of air, did not change the catalyst activity at all.
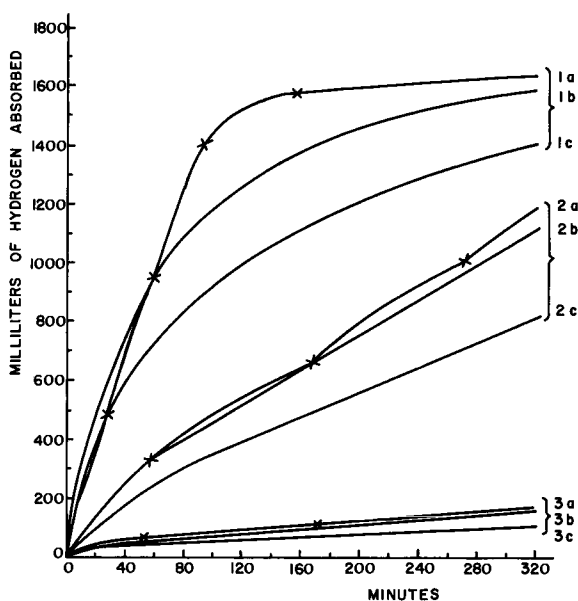
FIG. 2. Effect of oxygen on the rate of hydrogenation of heptaldehyde (one mole $H_2 \equiv$ 600 ml at 25°C): (1) 5% ruthenium-on-carbon, 1000 mg, (2) 5% platinum-on-carbon, 1000 mg, and (3) platinum oxide, 59.7 mg; (a) intermittent shaking with air, (b) 1% oxygen (as air) in hydrogen, and (c) no oxygen; $\times$ = hydrogen removed and solution shaken with air for 2 minutes. Solvent: 44.5% v/v aqueous ethanol.

Increased catalytic activity may also be obtained by adding oxygen initially to the hydrogen. Curves 1b, 2b, and 3b of Fig. 2 are the rate curves for ruthenium-on-carbon, platinum-on-carbon, and platinum oxide when 1% oxygen, as air, was added initially to the hydrogen. No appreciable part of the hydrogen absorption was due to oxidation of hydrogen, and the oxygen content increased as the reaction progressed. Rates obtained with 0.5% and 2.0% oxygen were only slightly less than those obtained with 1.0% oxygen, but with 3.0% oxygen the rates were definitely lower. The beneficial effect of oxygen on the rate of hydrogenation is not general. A series of experiments, using 5% platinum-on-carbon and 5% ruthenium-on-carbon with 0.5% and 1% oxygen in hydrogen, was made with octene-1, 1-nitropropane, benzaldehyde, and cyclohexanone as substrates. Only with benzaldehyde were there improvements in rate, and those were smaller than with heptaldehyde. Oxygen caused a definite decrease in rate when the substrate was octene or nitropropane, and was without effect with cyclohexanone.

C. PALLADIUM CATALYSTS

Palladium catalysts are not very active for hydrogenation of saturated aliphatic aldehydes, and have in fact frequently proved useful for reductions

in which the aldehyde function was to be preserved. Nonetheless, palladium has been used in reduction of various aliphatic aldehydes with success. For instance, hydrogenation over palladium-on-carbon of the dialdehyde, D'-methoxy-D-hydroxy-methyldiglycolic aldehyde (I), effects preferential reduction of only one aldehyde group. The hydrogenation carried out in absolute ethanol at 1200 psig with a 50 % catalyst loading based on substrate required 15 hours for completion. Over Raney nickel both aldehyde functions were reduced. The authors suggested that preferential reduction over palladium is due to the fact that the aldehyde does not react as such, but in a cyclized form in which one aldehyde has formed a hemiacetal (II). Dialdehydes that do not possess a free hydroxyl group, and therefore cannot undergo similar cyclization, are not reduced under the same conditions where I is converted to III. The authors suggested that dialdehydes lacking a suitable hydroxyl are mutually involved in the formation of a 1,4-dioxane ring system (Cadotte *et al.*, 1957).

$$
\begin{array}{ccc}
\text{CH}_2\text{OH} & & \text{CH}_2 \\
\text{CHO} \quad \text{H} \quad \text{O} \quad \text{H} & & \text{CHO} \quad \text{H} \quad \text{O} \quad \text{H} \\
\text{CHO} \quad \text{OCH}_3 & \rightleftharpoons & \text{O} \quad \text{OCH}_3 \quad \rightarrow \\
& & \text{CHOH} \\
(\text{I}) & & (\text{II})
\end{array}
$$

$$
\begin{array}{c}
\text{CH}_2\text{OH} \\
\text{CH}_2\text{OH} \quad \text{H} \quad \text{O} \quad \text{H} \\
\text{OCH}_3 \\
\text{CHO} \\
(\text{III})
\end{array}
$$
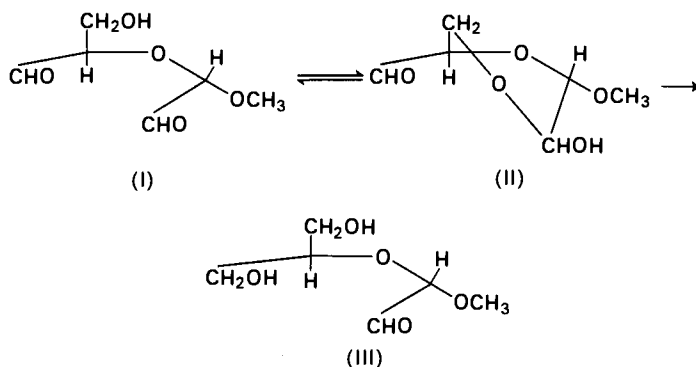
Phenylacetaldehyde, which might be expected to behave as an aliphatic aldehyde, was reduced over colloidal and supported palladium under conditions where other aliphatic aldehydes were unaffected. Perhaps reduction of phenylacetaldehyde occurs through the enol form. Hydrogenations were carried out in acetone, water, ethanol, and acetic acid; the rate was greatest in acetone. The solvent was said to affect the rate of hydrogenation by changing the surface of the catalyst through lyosorption, thus influencing the hydrogen adsorption on the catalyst (Csuros and Sello, 1949).

An interesting example of successful use of a palladium catalyst is in the synthesis of butyrolactone (VI) by selective hydrogenation of β-cyanopropionaldehyde (IV) to the cyano alcohol (V) followed by hydrolysis. The reductions were carried out at 300–4500 psig and room temperature. Higher temperatures favor reduction of both functions. Every trace of alkali must be rigorously excluded from the system to obtain adequate selectivity. In an example, 25 gm β-cyanopropionaldehyde in 100 ml water was reduced over

2.2 gm 5% palladium-on-carbon at room temperature and 1800 psig. The reduction ceased spontaneously. After hydrolysis of the nitrile, 14.5 gm butyrolactone was obtained (Komatsu et al., 1964).

$$NCCH_2CH_2CHO \xrightarrow{H_2} NCCH_2CH_2CH_2OH \xrightarrow{H_2O}$$

(IV)   (V)   (VI)
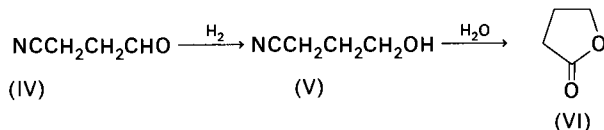
Aldehydes with a tendency to exist in the enol form may undergo hydrogenolysis over palladium catalysts. The reduction has served as a means of introducing a methyl group. For instance, 17,17-ethylenedioxy-5α-androstan-3-one (VII) was treated with sodium formate in the presence of sodium methoxide, and the resulting formyl derivative hydrolyzed to obtain 2-formyl-5α-androstane-3,17-dione (VIII). Selective hydrogenation of VIII over 10% palladium-on-carbon in ethanol-hydrochloric acid afforded 2α-methyl-5α-androstane-3,17-dione (IX) in 65% yield (de Ruggieri, 1965).

(VII)   (VIII)   (IX)
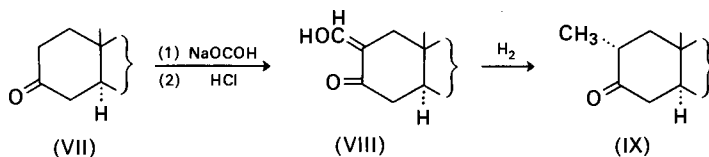
D. PLATINUM CATALYSTS

Platinum oxide was at one time the preferred catalyst for hydrogenation of aliphatic aldehydes. Although this catalyst is easily deactivated when used in hydrogenation of aldehydes, it may be stabilized by appropriate additives or, when deactivated, easily regenerated by shaking the mixture with air. Supported platinum catalysts make much better use of the metal (see Fig. 2) and for reasons of economy are preferred to platinum oxide. The activity of supported platinum catalysts, like unsupported platinum, may be increased by periodic regeneration of the catalyst by shaking the reaction mixture with air.

Hydrogenation of aldehydes over platinum catalysts, particularly platinum oxide, seems best carried out in the presence of a promoter, such as ferrous chloride (Carothers and Adams, 1923) or stannous chloride (Maxted and Akhtar, 1959). For example, it was not possible to reduce heptaldehyde in ethanol over platinum oxide without repeated reactivation of the catalyst by air, but in the presence of as little as 0.005 mole of ferrous chloride per mole of platinum oxide the reduction proceeded rapidly without deactivation of the catalyst (Carothers and Adams, 1923). However, the reduction still stopped prematurely with 20% of the aldehyde unreduced; the iron salt

catalyzed the interaction of the ethanol solvent with heptaldehyde, forming an acetal that was not reduced under the conditions of the reaction. The use of 70% aqueous ethanol diminished this effect but did not eliminate it entirely.

A practical use has been made of the interaction of aldehydes and alcohols by providing, through hydrogenolysis, a general synthesis of ethers. Hydrogenation of aldehydes, and more particularly ketones, in acidic alcohol over platinum oxide gives ethers in fair to excellent yield. Reduction over platinum oxide of isobutyraldehyde, in a 15 molar excess of methanol containing dry hydrogen chloride, gave isobutyl methyl ether in 48% yield (Verzele et al., 1963).

$$CH_3 \diagdown \atop CH_3 \diagup CHCHO + CH_3OH \longrightarrow CH_3 \diagdown \atop CH_3 \diagup CHCH_2OCH_3$$
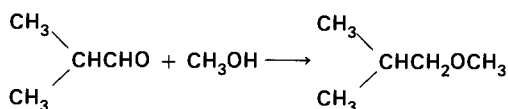
Platinum oxide has been used successfully under widely different reaction conditions for reduction of streptomycin. Streptomycin sulfate, hydrogenated in water over platinum oxide or 5% palladium-on-carbon at 750–900 psig, afforded dihydrostreptomycin in nearly quantitative yields (Biniecki et al., 1956). Only atmospheric pressure was used to reduce a double salt of streptomycin over platinum oxide in butanol-water (Ikeda et al., 1953). A number of satisfactory procedures using platinum metal catalysts have been worked out for this reduction, but remain largely proprietary.

The differences in activity between palladium and platinum oxide for hydrogenation of aliphatic aldehydes have been used as an aid in proof of structure. The aldehyde (X), obtained by base-catalyzed cyclization, was first shaken with hydrogen over palladium-on-carbon. No hydrogen was absorbed, indicating that X contained no carbon–carbon double bonds. Over platinum oxide, X absorbed exactly one equivalent of hydrogen with formation of the alcohol (XI) (Moe et al., 1951).
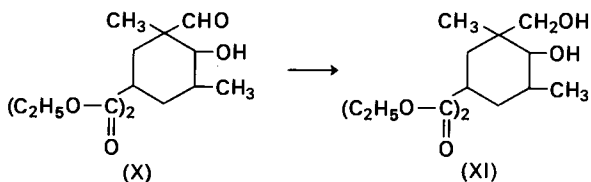
Hydrogenation of the aliphatic nitroaldehyde, 4-nitro-1-hexanal, to 4-amino-1-hexanol provides an example of what is probably a selective hydrogenation of an aldehyde function in the presence of a nitro group. It might be assumed that, if the nitro group were reduced first, interaction of the resulting amine and aldehyde would produce α-ethylpyrrolidine by cyclization or polymers by intermolecular condensation. In fact, when the

reduction was carried out at 125°C over Raney nickel, the products were ethylpyrrolidine and unidentified high-boiling material. Hydrogenation of 14.5 gm 4-nitro-1-hexanal in 100 ml absolute ethanol over 1.3 gm platinum oxide (added in two portions) resulted in absorption of approximately 3.8 moles of hydrogen and formation of 4-amino-1-hexanol, obtained in 73% yield after distillation (Warner and Moe, 1952).

$$C_2H_5CHCH_2CH_2CHO \longrightarrow C_2H_5CHCH_2CH_2CH_2OH$$
$$\quad\quad | \quad\quad\quad\quad\quad\quad\quad\quad\quad | $$
$$\quad\quad NO_2 \quad\quad\quad\quad\quad\quad\quad\quad NH_2$$
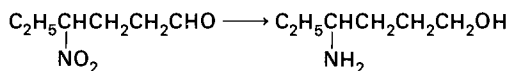
E. RUTHENIUM CATALYSTS

Ruthenium makes an excellent catalyst for hydrogenation of aliphatic aldehydes in both continuous and batch processing (Rylander et al., 1963a) but, despite this, has been seldom used. Figure 2 shows the superiority of ruthenium-on-carbon over platinum-on-carbon and over platinum oxide, the catalyst most used in hydrogenation of aliphatic aldehydes. Ruthenium shows to especial advantage in this comparison, because of the aqueous medium; the presence of water is known to accelerate markedly the rate of hydrogenation of many substrates over ruthenium (Rylander et al., 1963b). It is perhaps because ruthenium functions so well in water that it has proved to be an exceptional catalyst for hydrogenation of various carbohydrates. One such use of ruthenium catalysts is in production of polyhydric alcohols by simultaneous hydrolysis and hydrogenation of polysaccharides. Almost quantitative yields of polyhydric alcohols are obtained directly from materials such as cellulose (Sharkov, 1963). The reduction is thought to go so well because the relatively unstable monosaccharides are removed by hydrogenation as rapidly as they are formed. Pentitols and hexitols in 95% yield were obtained by phosphoric acid-catalyzed hydrolysis and ruthenium-on-carbon-catalyzed hydrogenation of spruce wood sawdust. The transformations were carried out at 160–170°C and 450–750 psig. Sorbitol in yields of 90–100% was similarly obtained by hydrogenation of cotton. Carbon was found to be a better support for ruthenium than barium sulfate, and phosphoric acid proved more satisfactory than sulfuric acid. The product contained about 25–40% of sorbitan when sulfuric acid was used. Ruthenium gave much better yields of sorbitol than palladium or platinum (Balandin et al., 1959).

Ruthenium-on-carbon is an excellent catalyst for hydrogenation of dextrose to sorbitol in both continuous and batch processing (Boyers, 1959). The reductions are best carried out at elevated temperatures (100–180°C) and pressures (500–2000 psig). Permissible temperatures for satisfactory products depend in part on the equipment used for the reductions. In a

rocking bomb, where reductions are relatively slow, charring occurs at temperatures that in a vigorously stirred autoclave afford a high quality product. Sorbitol produced by ruthenium catalysis is removed directly from the reactor as a colorless liquid, uncontaminated by dissolved metal ions (Rakoncza and Knittel, 1963). Ruthenium catalysts promoted by palladium have also been used for hydrogenation of glucose to sorbitol (Cohn, 1960). In an example, 35 gm D-glucose was hydrogenated at 1000 psig and 126°C over a 1.6% ruthenium, 3.4% palladium-on-carbon catalyst in 65 gm water to produce a product containing 97.95% sorbitol.

Halogenated alcohols have been obtained in excellent yield by hydrogenation of halo aldehydes or their acetals over ruthenium catalysts. For example, 126 gm of the cyclic acetal (XII), prepared from hydrogen chloride, acrolein, and neopentylene glycol, was hydrogenated over 5 gm ruthenium-on-carbon at 85°C in 25 gm water containing 0.4 gm p-toluenesulfonic acid. The yield of trimethylene chlorohydrin (XIII) was quantitative (Belgian Patent 634845).

$$ClCH_2CH_2CH\begin{matrix}OCH_2\\ \\OCH_2\end{matrix}C\begin{matrix}CH_3\\ \\CH_3\end{matrix} \longrightarrow ClCH_2CH_2CH_2OH$$

(XII)   (XIII)
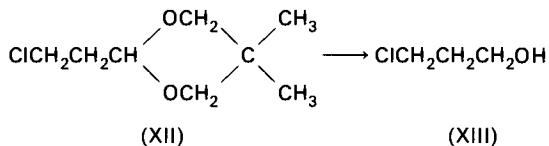
II. AROMATIC ALDEHYDES

Aromatic aldehydes can be reduced readily to the corresponding alcohol and, if the reduction is continued, to the hydrocarbon. Excellent yields of alcohol may be obtained if the reduction is interrupted after absorption of one equivalent of hydrogen, indicating that the hydrocarbon arises primarily from the alcohol and not directly from the aldehyde in one step. Some kinetic evidence also supports this view (Meschke and Hartung, 1960).

A. PALLADIUM CATALYSTS

Palladium makes the most active catalyst for reduction of aromatic aldehydes under mild conditions. The rates of hydrogenation at room temperature and atmospheric pressure of benzaldehyde, furfural, salicylaldehyde, and o-chlorobenzaldehyde over 5% palladium-, platinum-, rhodium-, and ruthenium-on-carbon were measured in a number of solvents, and in every case palladium was more active than other catalysts (Southwick and Coven, 1962). In another comparison, platinum oxide and palladous oxide showed roughly equivalent activities in hydrogenation of several aromatic aldehydes;

the relative effectiveness of the catalysts varied with the substrate (Shriner and Adams, 1924). In still another comparison, supported palladium and platinum catalysts were shown to be more active than unsupported catalysts. Palladium or platinum supported on carbon was more efficient than on alumina, zinc carbonate, calcium carbonate, or Super-cell (Cheronis and Levin, 1944).

Palladium is more active than other platinum metals for hydrogenation of benzyl alcohols (Rylander and Steele, 1965), and reductions of aromatic aldehydes over palladium will continue on to the hydrocarbon unless the reduction is stopped at absorption of one equivalent of hydrogen. For instance, reduction of β-naphthaldehyde over platinum oxide promoted by ferric chloride afforded β-hydroxymethylnaphthalene in 80% yield, whereas reduction over palladium-on-barium sulfate resulted in β-methylnaphthalene (Campbell et al., 1940).

Iron salts may also serve as promoters in reduction of certain aldehydes over palladous oxide. The additive was effective in increasing the rate of reduction only in those aldehydes, such as salicylaldehyde and vanillin, having a free hydroxyl group; ethers derived from them and aldehydes devoid of hydroxyl functions were unaffected by the promoter (Shriner and Adams, 1924). The yield of alcohol from hydrogenation of certain activated aromatic aldehydes may be decreased through intermolecular condensation as well as overhydrogenation. For instance, hydrogenation of vanillin (XIV) over 10% palladium-on-carbon in acetic acid gave 2-methoxy-4-methyl-phenol (XV) in 40% yield and a condensation product (XVI) in 25% yield (St. Pfau, 1939).
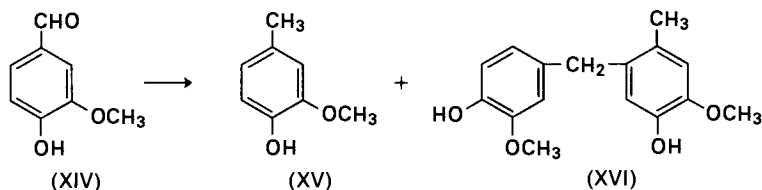
B. PLATINUM CATALYSTS

Aromatic as well as aliphatic aldehydes rapidly deactivate platinum oxide catalysts, apparently by reducing the catalyst to a lower, inactive oxidation state. Activity may be restored by shaking the reaction mixture with air, and loss of activity prevented by addition of various additives to the reaction mixture. For instance 3-methoxy-6-bromobenzaldehyde (XVII) was reduced to the corresponding benzyl alcohol (XVIII) over platinum oxide–iron by shaking a solution of 24 gm XVII in 150 ml alcohol with 0.1750 gm platinum

oxide and 0.013 gm ferrous chloride under 1 atm hydrogen pressure until absorption ceased (Gardner and McDonnell, 1941). The reduction is notable in that dehydrohalogenation was kept to low levels. No comparison of catalysts was made in this work, but it is probably safe to assume that palladium catalysts would have caused considerable loss of halogen. Other examples of preservation of halogen during reduction of halo·aldehydes óver platinum oxide have been reported by Carothers and Adams (1924).

(83% yield)

(XVII)   (XVIII)
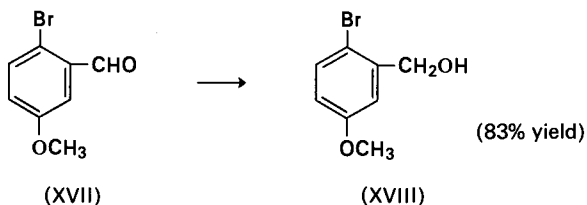
The reduction of furfural over platinum oxide further illustrates the role of additives in the maintenance of catalyst activity. Furfural is reduced quantitatively to furfuryl alcohol in ethanol over platinum oxide-iron, if the reduction is stopped after absorption of one equivalent of hydrogen. Further absorption gives a mixture of products. Frequent air reactivation is necessary unless the catalyst is promoted by ferrous chloride, a material that in increasing amounts changes from a promoter to a poison (Kaufmann and Adams, 1923).

C. RUTHENIUM CATALYSTS

Ruthenium has been little used for reduction of aromatic aldehydes. Under mild conditions ruthenium is not nearly so active as palladium, but as increasingly vigorous conditions are used ruthenium gains in relative merit. Ruthenium catalysts have been shown to have a high activity in reduction of furfural and, of considerable value, the activity was maintained through many reuses. The reductions were carried out in an alcohol solvent with 0.5–1.5% catalyst calculated as percent by weight of metal based on substrate. Reduction of furfural over 5% ruthenium-on-carbon at room temperature and 1400 psig gave an 83% yield of furfuryl alcohol. As the temperature was raised more ring saturation occurred. Tetrahydrofurfuryl alcohol was formed in 89% yield by reduction of furfural over ruthenium dioxide at 100°C and 1400 psig (Ponomarev and Chegolya, 1962). Furfural was reduced to tetrahydrofurfuryl alcohol in 77% yield, after distillation, over ruthenium dioxide in ethanol containing magnesium oxide at 110°C and 2250 psig (Howk, 1949).

D. SOLVENT

The rates of hydrogenation of aromatic aldehydes to alcohols and of the alcohols to hydrocarbons are both influenced by the solvent. The rate of hydrogenation of benzaldehyde to benzyl alcohol over 5% palladium-on-carbon decreased with the solvent in the order, acetic acid > methanol > ethyl acetate > hexane > dimethylformamide > benzene > water. In benzene, hexane, ethyl acetate, and dimethylformamide the rate of reduction declined abruptly to a low value after absorption of one equivalent of hydrogen but, in methanol and acetic acid, absorption of the second equivalent continued at a lower, gradually declining, but still very appreciable rate (Southwick and Coven, 1962). High yields of benzyl alcohol could therefore be obtained in methanol and acetic acid only by interrupting the reduction after absorption of one equivalent.

The rate of hydrogenation of benzaldehyde over platinum oxide decreased with solvent in the order, acetone > acetic acid > ethyl acetate > petroleum ether > ethyl ether > pyridine > benzene, and for the last four solvents was extremely low (Carothers and Adams, 1924). This order changes with substrate and cannot be generalized. Ethyl alcohol has been recommended as a good solvent for most reductions of aldehydes (Carothers and Adams, 1924). Piperonal was reduced in a number of solvents and the rate fell in the order, ethanol > isopropanol > esters > ethers > hydrocarbons (Cheronis and Levin, 1944).

Meschke and Hartung (1960) showed that the rate of reduction of benzaldehyde to benzyl alcohol in ethanol with a palladium-on-carbon catalyst was zero order with respect to substrate, but that the hydrogenolysis step, benzyl alcohol to toluene, rapidly declined in rate as the reaction progressed. The hydrogenolysis was inhibited by toluene and the addition of toluene caused further inhibition, although the additional toluene was without effect on the rate of the first step. Over platinum oxide the reduction of benzaldehyde in absolute ethanol ceased after absorption of one equivalent of hydrogen, but in 95% ethanol continued with slow formation of toluene (Carothers and Adams, 1924).

Hydrogenation of aldehydes in methanol may be complicated by acetal formation catalyzed by traces of acid. For example, in technical methanol, hydrogenation of benzaldehyde stopped at 70% of the theoretical absorption. The aldehyde had completely disappeared, for the unreduced portion has been converted to an acetal. Little or no acetal formation occurred when ethanol was the solvent (Carothers and Adams, 1924).

III. UNSATURATED ALDEHYDES

Unsaturated aldehydes may be reduced at either or both points of unsaturation. Any of the several possible products usually may be made

the major one by a proper selection of reaction variables, including such diverse factors as solvent, metal, support, reaction conditions, and the effective but highly empirical use of catalyst modifiers. The products of hydrogenation are determined also by the structure of the substrate, which influences the relative accessibility of the catalyst to each function. Conjugated and unconjugated unsaturated aldehydes behave differently, and the further distinction may be made between those conjugated aldehydes that are vinylogs of aliphatic aldehydes and those that are vinylogs of aromatic aldehydes. For example, the carbonyl function of crotonaldehyde is rarely reduced over palladium, whereas in hydrogenations of cinnamaldehyde at least some carbonyl reduction usually occurs. This difference in behavior can be rationalized by the knowledge that palladium is a poor catalyst for hydrogenation of aliphatic aldehydes, but excellent for hydrogenation of aromatic aldehydes. Cinnamaldehyde is a vinylog of benzaldehyde, and its carbonyl function might consequently be expected to be much more readily reduced than that in crotonaldehyde.

A. ALIPHATIC UNSATURATED ALDEHYDES

Hydrogenation of unhindered aliphatic α,β-unsaturated aldehydes usually proceeds with the selective hydrogenation of the carbon–carbon double bond. Over palladium the reduction stops spontaneously with the formation of the saturated aldehyde. In a large number of experiments with palladium on various supports and in various solvents, crotonaldehyde was reduced only to butyraldehyde, with one exception (Rylander and Himelstein, 1964). Remarkably, the only hydrogenations using crotonaldehyde in which some of the carbonyl function was reduced were over palladium-iron catalysts, the same catalysts that prevented aldehyde reduction with cinnamaldehyde.

Under certain conditions an unhindered α,β-unsaturated aldehyde may be reduced to an unsaturated alcohol. However, accomplishing such a reduction may prove to be a formidable task, for most hydrogenations will not follow this course. Tuley and Adams (1925) reduced cinnamaldehyde to cinnamyl alcohol in ethanol over an unsupported platinum–zinc–iron catalyst, and this same catalyst system was found later to afford high yields of 2-butene-1-ol from crotonaldehyde (Rylander et al., 1963a).

$$CH_3CH = CHCHO + H_2 \longrightarrow CH_3CH = CHCH_2OH$$
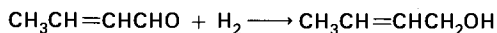
The platinum–iron–zinc system was also found to produce the unsaturated alcohol when platinum was supported (Table I). The support was specific: carbon and calcium carbonate produced 2-butene-1-ol on hydrogenation of crotonaldehyde (experiments 1 and 2), whereas butyraldehyde was formed

TABLE 1

CATALYTIC HYDROGENATION OF CROTONALDEHYDE AND CINNAMALDEHYDE[a]

Experiment	Catalyst	Amount of catalyst (mg)	Atoms of metal[b] per atom of Pt		Substrate (0.1 mole)	Solvent (50 ml)	Product
1	5% Pt/C	2000	0.4 Fe	0.06 Zn	Crotonaldehyde	Ethanol	2-Butene-1-ol
2	5% Pt/CaCO₃	1000	3.75 Fe	0.12 Zn	Crotonaldehyde	Ethanol	2-Butene-1-ol
3	5% Pt/C	2000	0.4 Fe	0.06 Ag	Crotonaldehyde	Ethanol	2-Butene-1-ol
4	5% Pt/BaSO₄	2000	0.4 Fe	0.06 Zn	Crotonaldehyde	Ethanol	Butyraldehyde
5	5% Pt/Al₂O₃	2000	0.4 Fe	0.06 Zn	Crotonaldehyde	Ethanol	Butyraldehyde
6	5% Pt/C	2000	0.4 Fe	0.06 Ag	Cinnamaldehyde	Hexane	Cinnamyl alcohol
7	10% Pt/C	1000	0.4 Fe	0. 6 Zn	Crotonaldehyde	Ethanol	2-Butene-1-ol
8	30% Pt/C	300	0.4 Fe	0.06 Zn	Crotonaldehyde	Ethanol	2-Butene-1-ol
9	PtO₂	200	0.25 Fe	0.04 Zn	Cinnamaldehyde	Hexane	Cinnamyl alcohol
10	5% Pt/C	2000	0.4 Fe	0.06 Zn	Cinnamaldehyde	Hexane	Cinnamyl alcohol

[a] Temperature: 25°C; pressure: 50 psig.
[b] Iron was added as ferrous chloride, zinc as zinc acetate, and silver as silver nitrate.

over barium sulfate and alumina (experiments 4 and 5). Efforts to alter the course of the reaction over barium sulfate and alumina supports, by increasing the amounts of promoters, had as their only effect the poisoning of the catalysts. The metal concentration on the carrier does not appear to be critical, and 2-butene-1-ol was obtained with 5%, 10%, and 30% platinum-on-carbon.

It was necessary in all experiments with crotonaldehyde using zinc or iron to have both present simultaneously if selective reduction of the carbonyl was to be achieved. These metals are quite specific and many futile attempts were made to replace iron and/or zinc as a promoter. It was found that silver could replace zinc, but no other substitution gave the desired result. Without iron present, silver- and/or zinc-promoted platinum gave only butyraldehyde. Numerous experiments were also made in efforts to find conditions under which palladium, rhodium, or ruthenium could be used as a catalyst for selective hydrogenation of the carbonyl group. Many metal modifiers such as iron, zinc, gold, silver, tin, calcium, copper, nickel, and lead were tried, singly or in combination, but in every experiment butyraldehyde was the only product.

Selective reduction of the aldehyde function in crotonaldehyde over platinum–iron–zinc catalysts seems to be possible because of the proximity of the functional groups. When the two functional groups were very far apart, as in a mixture of cyclohexene and butyraldehyde, it was not possible to obtain selective reduction of the aldehyde; the olefin was reduced preferentially (Rylander *et al.*, 1963a; Rylander and Himelstein, 1964).

With crotonaldehyde the reduction usually stopped before absorption of one equivalent of hydrogen, necessitating reactivation of the catalyst. Reactivation was readily accomplished by removing the hydrogen and shaking the reaction mixture for a few minutes with air. The procedure returned the catalyst to its original activity when the solvent was ethanol, but had little effect on a deactivated catalyst when the solvent was hexane. Hexane was therefore not a suitable solvent for hydrogenation of crotonaldehyde, but cinnamaldehyde was smoothly reduced to cinnamyl alcohol in hexane solvent since regeneration was not necessary.

An iron–zinc–platinum catalyst has been used for selective hydrogenation of 2-ethyl-2-hexenal-1 to the unsaturated alcohol. The catalyst contained 0.6 mole of ferrous chloride and 0.05 mole of zinc acetate per mole of platinum oxide. In an example, 232 gm 2-ethyl-2-hexenal-1 in 232 gm isopropanol was reduced over 1 gm of this catalyst at 20–40°C and 60 psig to give the unsaturated alcohol in 79% yield and 62% conversion (German Patent 1,158,960).

$$CH_3CH_2CH_2CH = \underset{\underset{C_2H_5}{|}}{C} - CHO \longrightarrow CH_3CH_2CH_2CH = \underset{\underset{C_2H_5}{|}}{C} - CH_2OH$$
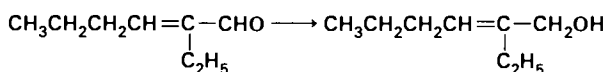
As the carbon–carbon double bond becomes more highly substituted, selective reduction of the aldehyde function becomes easier. For instance, selective reduction of a 6-formyl group over palladium was used in the preparation in good yield of the 6-hydroxymethyl 3-enol ethers derived from cortisone acetate, deoxycorticosterone acetate, and androst-4-ene-3,17-dione.
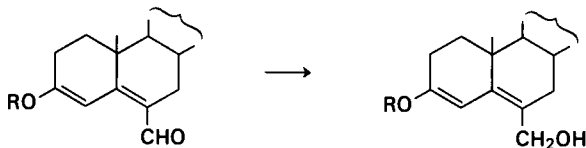
The hydrogenations were carried out over 5% palladium-on-carbon in methanol containing sodium acetate, and were stopped after absorption of one equivalent of hydrogen (Burn *et al.*, 1964).

Citral (XIX), carrying two trisubstituted double bonds, was selectively reduced to geraniol (XX) in ethanol over platinum oxide containing an iron promoter. Iron was necessary to prevent deactivation of the catalyst. If the reduction were continued, citronellol (XXI) and finally tetrahydrogeraniol (XXII) were produced selectively in sequence (Adams and Garvey, 1926).
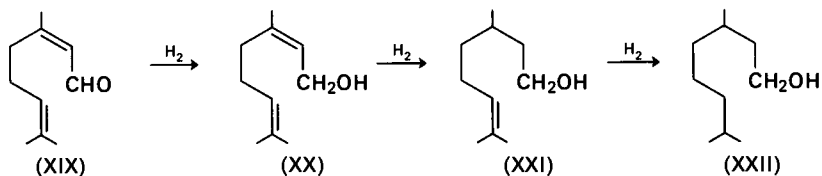
Ruthenium catalysts promoted by lead, silver, cadmium, bismuth, or mercury have been used in similar reductions. Citronellol has been obtained in high yield by hydrogenation of citronellal in water over a ruthenium–lead-on-carbon catalyst at 65°C and 1500 psig (Japanese Patent 25654/63).

B. Aromatic Unsaturated Aldehydes

The reduction of aromatic α,β-unsaturated aldehydes is attended by a number of complications. Considering cinnamaldehyde as a model, the possible reduction products excluding bimolecular and ring-saturated products, are hydrocinnamaldehyde, cinnamyl alcohol, phenylpropanol, phenylpropene, and phenylpropane. Using colloidal palladium, after absorption of one mole of hydrogen, Skita found nearly pure hydrocinnamaldehyde (Skita, 1915). However, later workers, repeating these experiments, found instead of this aldehyde a mixture of unchanged aldehyde, saturated alcohol, and phenylpropane (Straus and Grindel, 1924). Still later workers obtained results agreeing with those of Skita (Bogert and Powell, 1931). No definitive answer is likely to be forthcoming as this reduction is unusually complicated.

The products obtained when the reduction of cinnamaldehyde came to a spontaneous stop were found to depend on the method of preparation of the catalyst (Keith, 1963), on the solvent, on the metal, on the supports, and on various additives (Rylander et al., 1963a; Rylander and Himelstein, 1964).

The effect of solvent on the yield of hydrocinnamaldehyde is shown in Table II. The remainder of the substrate was converted largely to phenylpropanol, except in acetic acid where appreciable phenylpropane formed.

TABLE II

HYDROGENATION OF CINNAMALDEHYDE IN VARIOUS SOLVENTS[a]

Solvent	Percent hydrocinnamaldehyde	Rate (ml H_2/minute)
Methanol	55	18
Ethanol	50	21
n-Propanol	57	8
Isopropanol	59	8
n-Butanol	54	9
Acetic acid	73	29
Hexane	—[b]	—
Triethylamine	66	4
Benzene	80	2
Ethyl acetate	74	3
Dimethylformamide	59	8
Water	88	3

[a] 200 mg 5% palladium-on-carbon, 2.00 ml cinnamaldehyde, 50 ml solvent; room temperature, atmospheric pressure.
[b] Rapid poisoning.

Table III shows the effect of support on the yield of hydrocinnamaldehyde and on the rate of reduction in various solvents. The support is clearly an important factor in determining the selectivity, but a correlation between the type of support, rate of reduction, solvent, and selectivity is not evident. The data establish that the course of reduction can be sharply changed, even though the criteria for selection are at present purely empirical.

Table IV gives data on the effect of additives on the course and rate of reduction of cinnamaldehyde. Hydrofluoric and hydrochloric acids are effective promoters for the reduction, while hydrobromic and hydroiodic acids are definitely poisons. The product composition has no apparent correlation with rate. The most interesting result was that obtained when using an appropriate amount of ferrous chloride as a promoter; only hydrocinnamaldehyde was obtained and at a very rapid rate. These selectivities were easily reproduced, but were specific for each palladium catalyst and varied with the activity of the catalyst. The 1:1 ratio of ferrous chloride to

TABLE III
Effect of Support on Hydrogenation of Cinnamaldehyde[a]

Support	Methanol		Ethanol		Acetic Acid	
	% HC	Rate (ml H$_2$/min)	% HC	Rate (ml H$_2$/min)	% HC	Rate (ml H$_2$/min)
Carbon	55	18	50	21	73	29
Barium sulfate	96	17	91	6	60	5
Barium carbonate	54	12	—[b]	—[b]	—[b]	—[b]
Calcium carbonate	72	16	95	4	54	11
Alumina	94	17	100	6	77	24
Kieselguhr	93	14	—[b]	—[b]	99	7
Magnesium carbonate	56	12	84	6	35	15

[a] 200 mg 5% palladium-on-support, 2.00 ml cinnamaldehyde, 50 ml solvent; room temperature, atmospheric pressure. % HC = Percent hydrocinnamaldehyde in product when reduction stopped spontaneously.

[b] Substantial poisoning.

TABLE IV
Effect of Additives on Hydrogenation of Cinnamaldehyde[a]

Additive	Moles additive per mole palladium	% HC	Rate (ml H$_2$/minute)
None	—	55	18
Hydrofluoric acid	5	83	47
Hydrochloric acid	5	54	40
Hydrobromic acid	5	68	5
Hydroiodic acid	5	—[b]	—[b]
Sodium hydroxide	20	65	4
Sodium pyrophosphate	2	48	30
Cupric acetate	2	—[b]	—[b]
Ferrous sulfate	1	85	12
Ferrous chloride	1	100	40
Ferrous chloride	2	86	40
Ferrous chloride	4	71	40
Ferrous chloride	0.5	70	27

[a] 2.00 ml cinnamaldehyde, 50 ml methanol, 200 mg 5% palladium-on-carbon; 1 atm, room temperature. %HC = Percent hydrocinnamaldehyde in product.

[b] Rapid poisoning.

palladium giving 100% hydrocinnamaldehyde was fortuitous; with other catalysts maximum selectivity occurred at other ratios, usually 1:0.9 to 1:1.3. It is interesting to contrast these results with those of Tuley and Adams (1925), who, using platinum catalysts, found iron additives to give

cinnamyl alcohol on absorption of one equivalent of hydrogen and not hydrocinnamaldehyde.

All the catalyst-solvent systems listed in Tables II, III, and IV produced at least 50% hydrocinnamaldehyde, but some systems produced chiefly phenylpropanol (Table V). The results with ferrous chloride (Table V) are particularly interesting when contrasted with the data in Tables III and IV. By using the palladium–iron catalyst in acetic acid instead of methanol, and palladium-on-kieselguhr in acidic instead of neutral methanol, an almost complete change in product composition can be achieved. The results in Table V from using large amounts of sodium pyrophosphate augment the data of Table IV, and show again that the product composition depends on the quantity of additive.

TABLE V

HYDROGENATION OF CINNAMALDEHYDE TO PHENYLPROPANOL[a]

Catalyst	Solvent	Additive	Percent Phenylpropanol	Rate (ml H_2/minute)
5% Pd/C	Methanol	1.0 gm sodium pyrophosphate	80	7
5% Pd/C	Acetic acid	1 mole $FeCl_2$/mole Pd	93	16
5% Pd/kieselguhr	Methanol	1 ml conc HCl	98	10

[a] 200 mg catalyst, 50 ml solvent; 1 atm, room temperature. The reported yields were from absorption measurements. Comparison of the infrared spectra of the products with known standards established that the values are approximately correct.

In addition to all the above mentioned variables, the product has been found to depend on the amount of catalyst used. Csuros (1948) found that, in the hydrogenation of cinnamaldehyde and the hydroxybenzaldehydes over palladium-on-carbon, the amount of catalyst could determine the product. Cinnamaldehyde could be selectively reduced at either point of unsaturation by controlling the amount of catalyst (Csuros, 1947; Csuros *et al.*, 1946).

Bogert and Powell (1931) obtained more satisfactory results in reducing a series of substituted cinnamaldehydes over colloidal palladium stabilized by gum arabic (Skita, 1915) than over platinum–zinc–iron catalysts (Tuley and Adams, 1925). The yield of phenylpropanes increased with an increase in hydrogenation pressure.

REFERENCES

Adams, R., and Garvey, B. S., *J. Am. Chem. Soc.* **48**, 477 (1926).
Balandin, A. A., Vasyunina, N. A., Chepigo, S. V., and Barysheva, G. S., *Dokl. Akad. Nauk SSSR* **128**, 941 (1959).

Biniecki, S., Kabzinski, A., and Muszynski, E., *Acta Polon. Pharm.* **13**, 135 (1956).

Bogert, M. T., and Powell, G., *J. Am. Chem. Soc.* **53**, 2747 (1931).

Boyers, G. G., U.S. Patent 2,868,847, January 13, 1959.

Burn, D., Cooley, G., Davies, M. T., Ducker, J. W., Ellis, B., Feather, P., Hiscock, A. K., Kirk, D. N., Leftwick, A. P., Petrow, V., and Williamson, D. M., *Tetrahedron* **20**, 597 (1964).

Cadotte, J. E., Dutton, G. G. S., Goldstein, I. J., Lewis, B. A., Smith, F., and Van Cleve, J. W., *J. Am. Chem. Soc.* **79**, 691 (1957).

Campbell, N., Anderson, W., and Gilmore, J., *J. Chem. Soc.* p. 819 (1940).

Carothers, W. H., and Adams, R., *J. Am. Chem. Soc.* **45**, 1071 (1923).

Carothers, W. H., and Adams, R., *J. Am. Chem. Soc.* **46**, 1675 (1924).

Carothers, W. H., and Adams, R., *J. Am. Chem. Soc.* **47**, 1047 (1925).

Cheronis, N. D., and Levin, N., *J. Chem. Educ.* **21**, 603 (1944).

Cohn, J. G. E., German Patent 1,082,245, May 25, 1960.

Csuros, Z., *Muegyet. Kozlemen.* p. 110 (1947).

Csuros, Z., *Magy. Kem. Lapja* **3**, 29 (1948).

Csuros, Z., and Sello, I., *Hung. Acta Chim.* **1**(4–5), 27 (1949).

Csuros, Z., Zech, K., and Geczy, I., *Hung. Acta Chim.* **1**, 1 (1946).

de Ruggieri, P., U.S. Patent 3,207,752, September 21, 1965.

Gardner, J. H., and McDonnell, T. F., *J. Am. Chem. Soc.* **63**, 2279 (1941).

Hoffman, N. E., Kanakkanatt, A. T., and Schneider, R. F., *J. Org. Chem.* **27**, 2687 (1962).

Howk, B. W., U.S. Patent 2,487,054, November 8, 1949.

Ikeda, H., Shiroyanagi, K., Ikeda, H., and Katayama, M., *J. Sci. Res. Inst.* (*Tokyo*) **47**, 52 (1953).

Kaufmann, W. E., and Adams, R., *J. Am. Chem. Soc.* **45**, 3029 (1923).

Keith, C. D., Unpublished observations, Engelhard Ind., 1963.

Koch, J. H., Jr., U.S. Patent 3,055,840, September 25, 1962.

Komatsu, T., Iwanaga, R., and Kato, J., U.S. Patent 3,141,895, July 21, 1964.

Maxted, E. B., and Akhtar, S., *J. Chem. Soc.* p. 3130 (1959).

Meschke, R. W., and Hartung, W. H., *J. Org. Chem.* **25**, 137 (1960).

Moe, O. A., Warner, D. T., and Buckley, M. I., *J. Am. Chem. Soc.* **73**, 1062 (1951).

Ponomarev, A. A., and Chegolya, A. S., *Dokl. Akad. Nauk SSSR* **145**, 812 (1962).

Rakoncza, N., and Knittel, D., Unpublished observations, Engelhard Ind., 1963.

Rylander, P. N., and Himelstein, N., *Engelhard Ind. Tech. Bull.* **4**, 131 (1964).

Rylander, P. N., and Kaplan, J., *Engelhard Ind. Tech. Bull.* **2**, 48 (1961).

Rylander, P. N., and Steele, D. R., *Engelhard Ind. Tech. Bull.* **6**, 41 (1965).

Rylander, P. N., Himelstein, N., and Kilroy, M., *Engelhard Ind. Tech. Bull.* **4**, 49 (1963a).

Rylander, P. N., Rakoncza, N., Steele, D., and Bolliger, M., *Engelhard Ind. Tech. Bull.* **4**, 95 (1963b).

St. Pfau, A., *Helv. Chim. Acta* **22**, 550 (1939).

Sharkov, V. I., *Angew. Chem. Intern. Ed. Engl.* **2**, 405 (1963).

Shriner, R. L., and Adams, R., *J. Am. Chem. Soc.* **46**, 1683 (1924).

Skita, A., *Ber. Deut. Chem. Ges.* **48**, 1685 (1915).

Southwick, A., and Coven, V., Unpublished observations, Engelhard Ind., 1962.

Straus, F., and Grindel, H., *Ann. Chem. Liebigs* **439**, 276 (1924).

Tuley, W. F., and Adams, R., *J. Am. Chem. Soc.* **47**, 3061 (1925).

Verzele, M., Acke, M., and Anteunis, M., *J. Chem. Soc.* p. 5598 (1963).

Voorhees, V., and Adams, R., *J. Am. Chem. Soc.* **44**, 1397 (1922).

Warner, D. T., and Moe, O. A., *J. Am. Chem. Soc.* **74**, 1064 (1952).

Willstätter, R., and Jaquet, *Ber. Deut. Chem. Ges.* **51**, 767 (1918).

15

Hydrogenation of Ketones

I. ALIPHATIC KETONES

The relative effectiveness of platinum metals for reduction of ketones depends largely on whether the ketone is aliphatic or aromatic and on the solvent. Palladium, for instance, is a poor catalyst for reduction of aliphatic but excellent for reduction of aromatic ketones, a distinction holding also for aliphatic and aromatic aldehydes. Hydrogenation of aliphatic ketones usually stops spontaneously at the alcohol stage with little danger of over-hydrogenation, except when special structural features are present.

A. CATALYSTS AND SOLVENTS

The rate of reduction of aliphatic ketones depends markedly on the catalyst and on the solvent. Table I shows the rates of hydrogenation of methyl isobutyl ketone, cyclohexanone, and cyclopentanone over 5% palladium-, platinum-, rhodium-, and ruthenium-on-carbon in various solvents (Breitner et al., 1959). Palladium was ineffective in all solvents tested. If the ketones were added dropwise instead of all at once to the palladium in solvent, hydrogenation proceeded at a slow but measurable rate. Platinum-on-carbon in aqueous acid hydrogenated all three compounds satisfactorily, but in base, poisoning occurred with cyclopentanone and methyl isobutyl ketone. The poison was formed during the hydrogenation and was not initially in the substrate; when the ratio of substrate and solvent to catalyst was doubled, the rate curve was unchanged. Some of these results have been reinterpreted, and the declining rates of hydrogenation were attributed to the low concentrations of ketone used in the study (Peterson and Casey, 1964). The effect of hydrochloric acid on the rate of reduction has also been shown to be related to the concentration of ketone; large promoting effects occur only at low concentrations of ketone. Aliphatic ketones were shown to be reduced over

TABLE I

RATE OF HYDROGENATION OF ALIPHATIC KETONES[a]

Catalyst	Solvent																	
	Acetic acid			Water			NaOH (0.5 N)			HCl (0.5 N)			Methanol			Ethyl acetate		
	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III
5% Pd/C	0.2	0.0	0.0	0.0	0.1	0.0	0.2	p′	0.2	0.0	0.1	0.1	0.0	0.2	0.0	0.0	0.1	0.0
5% Pt/C	0.2	7	0.3	6	22	18	p′	20	p′	11	22	10	0.2	0.2	0.3	0.2	0.3	0.2
5% Rh/C	0.2	11	p′	16	25	15	20	26	22	5	16	4	0.1	0.3	0.3	0.0	0.2	0.0
5% Ru/C	0.0	0.0	0.0	26	24	11	14	24	45	0.2	p′	0.2	p′	0.1	p′	0.0	0.1	0.0

[a] I = methyl isobutyl ketone, II = cyclohexanone, III = cyclopentanone. The rate is expressed in ml H_2/minute/300 mg catalyst; p′ indicates a slow decline in rate as the reaction progressed.

platinum catalysts in trifluoracetic acid at three times the rate obtained in acetic acid (Peterson and Casey, 1964), a fact which, together with others, lent support to the postulation that protonated ketones were intermediates in the hydrogenation (Brewster, 1954).

Rhodium and ruthenium, unlike platinum, were most active in neutral or basic solution and relatively slow in acid. In favorable environment both rhodium and ruthenium were exceptionally active, and appear to be desirable catalysts for this type of reduction. The statement had been made that rhodium would not hydrogenate ketones unless they were activated (Dunworth and Nord, 1952), a conclusion reached because alcohol was used exclusively as the solvent. Ruthenium has been little used in low pressure reductions of ketones, but has given some excellent results. Hydrogenation of 8 gm of ethyl-3-keto-10-acetoxydecanoate (I) in 90 ml absolute ethanol over 0.8 gm ruthenium oxide at 3 atm pressure afforded the hydroxy compound (II) in 90% yield (Smissman et al., 1964). This reduction showed an 8-hour induction period. Induction periods with ruthenium catalysts are common, especially in nonaqueous media at low pressure; at high pressures,

$$C_2H_5OCOCH_2\underset{\underset{(I)}{O}}{\overset{\|}{C}}-(CH_2)_6CH_2OCOCH_3 \longrightarrow C_2H_5OCOCH_2\underset{\underset{(II)}{OH}}{CH}-(CH_2)_6CH_2OCOCH_3$$
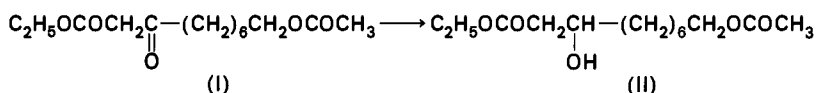
induction periods rarely occur regardless of solvent. Ruthenium catalysts are more commonly used at elevated pressure (Rapala and Farkas, 1958; Zirkle et al., 1961; Hasek et al., 1961). Catalytic reduction of 100 gm III in isooctane over 5% ruthenium-on-carbon at 100°C and 3000 psig allowed isolation of 32 gm cis and 54 gm trans amino alcohol (IV) (Hasek and Martin, 1963).
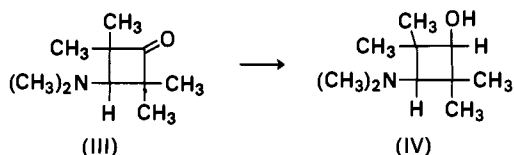
Rhodium is quite active for hydrogenation of ketones under mild conditions and has given some excellent results. Catalytic hydrogenation of (V) over 5% rhodium-on-carbon in acetic acid at 42 psig and room temperature gave stereoselectively a single 1-hydroxypyrrolizidine (VI) (Adams et al., 1960):
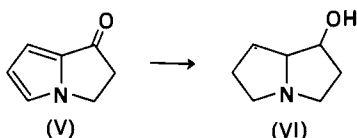
Unsuccessful attempts to reduce this substrate in the presence of platinum oxide or palladium-on-carbon have been reported (Clemo and Melrose, 1942). Similarly, VII was reduced to the alcohol (VIII) in 82 % yield over 5 % rhodium-on-alumina in acetic acid (Adams *et al.*, 1961; Nair and Adams, 1961).

(VII)   (VIII)
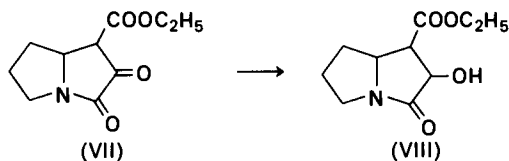
Promoters

Small quantities of acid or bases may have a marked effect on the reduction of a ketone, altering the rate or the product or both. It has been reported (Stacey and Mikulec, 1954) and confirmed (Hennion and Watson, 1958) that hydrogenation of 1-acetylcyclohexanol to the glycol was very slow over platinum oxide. The addition of acid completely suppressed reduction, but a small amount of ethanolic sodium hydroxide caused a marked acceleration in rate. Hydrogenation of 42.6 ml 1-acetylcyclohexanol over 0.30 gm platinum oxide in 75 ml ethanol containing 5 drops of 0.1 N ethanolic sodium hydroxide required 30 minutes for completion; without base the reduction took 3 hours. Other glycols were similarly prepared in excellent yield. The rates were not further accelerated by larger quantities of alkali. Traces
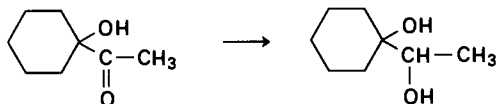
of acids commonly increase the rate of reduction, and may also exert either a beneficial or detrimental effect on the product, but it may be uncertain beforehand what the effect will be. Reduction of the keto lactone (IX) over platinum oxide in 30 ml methanol containing 2 drops of hydrochloric acid gave a crystalline hydroxy lactone (X), whereas without acid no crystalline compound could be obtained (Roy and Wheeler, 1963).

(IX)   (X)
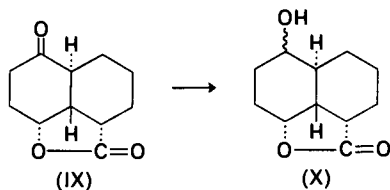
Hydrogenation of 2-acetobenzofuran over platinum oxide and over colloidal platinum resulted in different products, perhaps due to different

acidity levels in the two systems. Reduction over platinum oxide in ethanol gave a quantitative yield of 2-(1-hydroxyethyl)benzofuran, but over colloidal platinum, prepared by reduction *in situ* of chloroplatinic acid with liberation of hydrochloric acid, a mixture of products was obtained (Shriner and Anderson, 1939). [Traces of hydrochloric acid were shown later to have a marked effect on the reduction of coumaranone over platinum oxide (Shriner and Witte, 1941).] Hydrogenation of 2-acetobenzofuran over Raney nickel afforded the saturated alcohol.

$$\text{(benzofuranyl)}-\underset{\underset{\text{OH}}{|}}{\text{CH}}-\text{CH}_3 \xleftarrow{\text{RaNi}} \text{(benzofuranyl)}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\text{CH}_3 \xrightarrow{\text{PtO}_2} \text{(benzofuranyl)}-\underset{\underset{\text{OH}}{|}}{\text{CH}}-\text{CH}_3$$
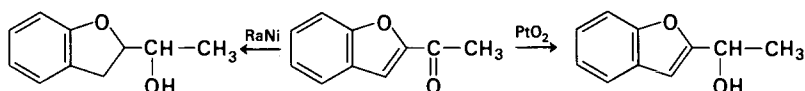
Small quantities of acids may promote side-reactions extrinsic to the hydrogenation. Reduction of cholestanone over platinum in glacial acetic acid containing hydrogen bromide gave an aldol coupling product, $C_{54}H_{90}O$, in about 40% yield. However, reduction over platinum in di-*n*-butyl ether containing a small amount of aqueous hydrobromic acid afforded mainly epicholestanol as the major product together with a small amount of cholestanol (Corey and Young, 1955).

B. HYDROGENOLYSIS

Ordinarily catalytic hydrogenations of aliphatic ketones stop cleanly at the alcohol stage with little or no hydrocarbon being formed. In acid solution, hydrogenolysis of ketones may be accentuated. Hydrogenation of acetone over platinum black in aqueous acidic medium gave isopropanol and propane, but in alkaline solution only isopropanol (Foresti, 1939). The amount of propane increased as hydrogen pressure decreased (Koizumi, 1940). Propane formation can be prevented by addition of small amounts of ferrous chloride to the catalyst (Carothers and Adams, 1925). Similarly, hydrogenation of cyclohexanone over platinum-on-pumice in an acid medium gave cyclohexanol and small quantities of cyclohexane; in alkaline solution only the alcohol was formed (Foresti, 1937). On the other hand, in a cyclohexanone derivative (XI), hydrogenolysis was extensive in neutral solution and somewhat diminished by use of a slightly acid medium. Hydrogenation of γ-(p-cyclohexanone)butyric acid (XI) over platinum oxide in water or absolute ethanol, platinum black in ethanol, or Raney nickel in ethanol or water resulted in mixtures containing small amounts of *cis*- and *trans*-hydroxycyclohexylbutyric acid (XII) and a large amount of cyclohexylbutyric acid. The best results were obtained when platinum oxide was used as the catalyst, and ethanol containing 1 drop of acetic acid or hydrochloric acid as the solvent (Dauben and Adams, 1948). The low percentage

of *cis* isomer and the extensive hydrogenolysis are surprising and anomalous features of this reduction. One might surmise that the reduction involved interaction of the two functional groups; models indicate *cis*-hydroxy-cyclohexylbutyric acid to be sterically disposed to form a virtually strainless lactone.
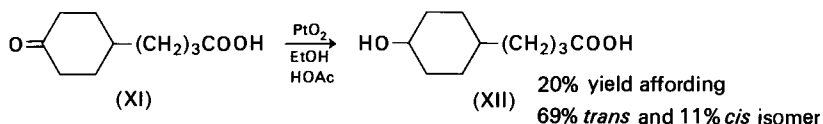
Ketones in the cyclitol series undergo a facile hydrogenolysis in mineral acid solution, a reaction first observed by Posternak (1941). Although the reduction was usually assumed to proceed in a straightforward manner, Post and Anderson (1962) showed it to be more complicated than had previously been recognized. Reduction of 3-O-methyl-D-*myo*-inosose-1 over platinum oxide in dilute sulfuric acid gave a mixture of four products, quebrachitol and (−)-bornesitol from reduction of the carbonyl, and quercitol methyl ether and the 1-methyl ether of (−)-cyclohexane-1,3/2,4-tetrol
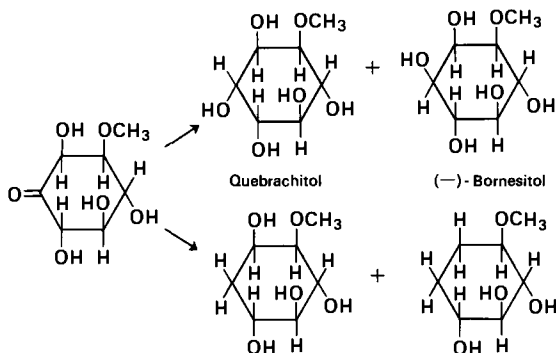
from hydrogenolysis. Similar results were obtained on reduction of D-*myo*-inosose-1 and 5-O-methyl-L-*myo*-inosose-1. On the other hand, *myo*-inosose-2 and DL-epiinosose-2 were converted nearly quantitatively to the monodeoxy compounds.

myo-inosose-2
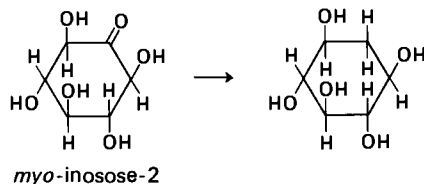
The authors point out that, in those inososes that gave a complex mixture of the hydrogenolysis products, one of the hydroxyls flanking the keto group is axial, while in the others both the flanking hydroxyls are equatorial. They tentatively suggest the generalization that the hydrogenolysis reaction

will proceed cleanly only if there are no axial hydroxyls adjacent to the keto group. In neutral solution the hydrogenolysis reaction is unimportant, and simple reduction of the carbonyl function occurs (Posternak, 1941).

Hydrogenolysis of ketones need not involve an alcohol intermediate. Hydrogenation of 29 gm ethyl acetoacetate over platinum black allowed isolation of 4 gm of the corresponding alcohol and 15 gm ethyl butyrate. The alcohol was shown not to be an intermediate in the formation of ethyl butyrate, for it remained unchanged when subjected to the same hydrogenation conditions. The course of reduction depended on the catalyst; no hydrogenolysis occurred when platinum black containing iron was used. The author (Faillebin, 1923) showed that the same products were obtained with unpromoted platinum from either the enol or ketone form.

$$CH_3CCH_2COC_2H_5 \quad \underset{\searrow}{\overset{\nearrow}{\longleftarrow}} \quad \begin{array}{c} CH_3CHCH_2COC_2H_5 \\ \overset{|}{OH} \quad \overset{\parallel}{O} \\[4pt] CH_3CH_2CH_2COC_2H_5 \end{array}$$
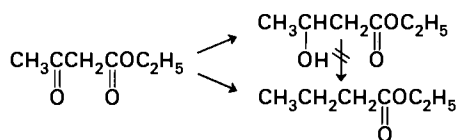
Some hydrogenolysis reactions of ketones seem to involve an enol form. Catalytic hydrogenolysis of 3-acyl oxindoles provides a general method for preparation of 3-alkyl oxindoles. The reductions were usually carried out over palladium oxide in ethanol, but with some substrates it was necessary to add acetic acid and to heat the reaction mixtures to about 50°C to ensure a smooth reduction. The facile hydrogenolysis of 3-acyl oxindoles was related to the enolic hydrogen atom in position 3; when this hydrogen was absent, as in 1,3-dimethyl-3-acetyl-oxindole, no reduction took place (Julian *et al.*, 1935).
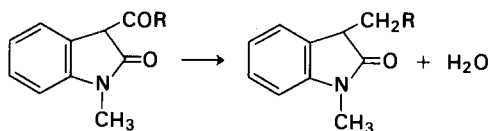
Hydrogenolysis of ketones may occur after interaction with an alcohol solvent, a sequence of reactions that provides a general synthesis of ethers. Ether formation probably proceeds through a hemiketal that undergoes hydrogenolysis. Yields of ethers range from fair to excellent; the side-products are paraffins and alcohols, arising probably from reduction of the ketone. Even ketones, which form ketals in only very low yield in equilibrium

$$\underset{R}{\overset{R'}{\diagdown}}C{=}O + R''OH \longrightarrow \underset{R}{\overset{R'}{\diagdown}}CH{-}O{-}R'' + H_2O$$
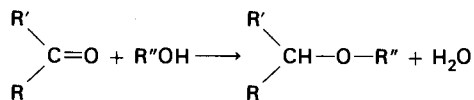
conditions, give satisfactory yields of ether. The reductions are carried out with a 15 molar excess of alcohol over platinum oxide in a solution made 2.5 molar with dry hydrogen chloride (Verzele et al., 1963). Ketals undergo hydrogenolysis to ethers in acid solution over, preferably, rhodium catalysts (Howard and Brown, 1961).

C. DIKETONES

Hydrogenation of diketones may afford diols, hydroxy ketones, or cyclic ethers. The products obtained depend both on the catalyst and on the substrate. Table II gives comparisons of 5 % palladium-, platinum-, rhodium-, ruthenium-, and iridium-on-carbon for selective hydrogenation of biacetyl, acetylacetone, and pentanedione-2,3 (Rylander and Steele, 1965). The relative activities of the catalysts and the selectivities achieved by each catalyst vary with the substrate. In the reduction of biacetyl, selectivity (to give the hydroxy ketone) fell in the order, palladium > rhodium > platinum ≅ ruthenium. That is, at comparable amounts of substrate remaining there was less fully reduced product with palladium than with other catalysts. Palladium was very active under the relatively vigorous conditions used; when less catalyst or milder conditions were used the reduction was sluggish. In partial hydrogenation of acetylacetone rhodium-on-carbon proved unique, combining an exceptionally fast rate with high yields of the intermediate product, 2-hydroxy-4-pentanone. One carbonyl of acetylacetone seems to be highly activated by the other, or perhaps the two together favor adsorption on the catalyst; when the reduction was carried out with acetone as a solvent the ketol was formed in high yield, and the acetone was recovered unchanged.

Hydrogenations of pentanedione-2,3 over palladium, rhodium, ruthenium, and iridium were either initially very sluggish or poisoned rapidly under both mild and vigorous conditions. Platinum-on-carbon, on the other hand, was an active catalyst in this reduction and gave good yields of a hydroxy ketone. Vapor phase chromatographic analysis indicated that only one of the two isomeric hydroxy ketones was formed, but it was undecided which isomer it was. In some substances the structure of the resulting ketol can be predicted with some assurance. Hydrogenation of 2,6,6-trimethyl-1,4-cyclohexanedione over platinum oxide in methanol afforded 2,6,6-trimethyl-4-cyclohexanol-1-one; the more highly hindered carbonyl remained unchanged (British Patent 790,607).
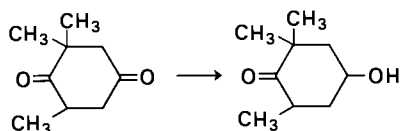
TABLE II

HYDROGENATION OF DIKETONE[a]

Catalyst	(mg)	Rate (ml H₂/min)	Temperature (°C)	Pressure (p.s.i.g.)	Dione (% by weight)	Hydroxyketone (% by weight)	Diol	
							dl (% by weight)	meso (% by weight)
Biacetyl								
5% Pd/C	600	246	102	1000	8	90	1	1
5% Pt/C	300	74	28	1030	28	25	24	23
5% Rh/C	300	112	26	525	10	72	8	10
5% Ru/C	300	108	100	1000	13	5	39	43
Acetylacetone								
5% Pd/C	300	7	102	510	64	34	2	2
5% Pt/C	300	16	26	510	83	9	8	8
5% Rh/C	300	320	26	510	2	90	8	8
5% Ru/C	300	16	26	510	68	16	16	16
5% Ir/C	300	20	26	510	84	7	9	9
Pentanedione-2,3								
5% Pd/C	1200	15	105	1000	20	80	0	0
5% Pt/C	300	54	27	510	10	85	<5	<5
5% Rh/C	1200	72	117	1010	90	10	0	0
5% Ru/C	600	<5	100	1010	80	20	0	0
5% Ir/C	300	<5	102	1010	85	15	0	0

[a] Solvent: cyclohexane. Some of the reductions were too fast to be easily stopped at the halfway point. Nonetheless a good idea of selectivity was obtained from most reductions regardless of where it was stopped, provided hydrogenation had not proceeded too far.

Hydrogenation of hexanedione-2,5 resulted only in 2,5-dimethyltetra-hydrofuran regardless of the catalyst used. No diol or ketol could be detected. Iridium-on-carbon proved to be exceptionally active for this reduction (Rylander and Steele, 1966), being 5–50 times more active than the other platinum metals. Thus, in the series biacetyl, acetylacetone, pentanedione-2,3, and hexanedione 2,5, the most active and/or selective catalyst was found to be different for each member.

Other workers have also noted marked differences in catalysts in hydrogenation of diketones. The 1,4-diketone, acoric acid (XIII), cyclized on hydrogenation over platinum oxide to form the ether (XIV) in good yield. No reduction of acoric acid occurred at all over 10% palladium-on-carbon in methanol or in methanol-hydrochloric acid (Birch et al., 1964), a result in keeping with the generally sluggish behavior of palladium catalysts in ketone hydrogenation under mild conditions. In a further example, the

(XIII)   (XIV)
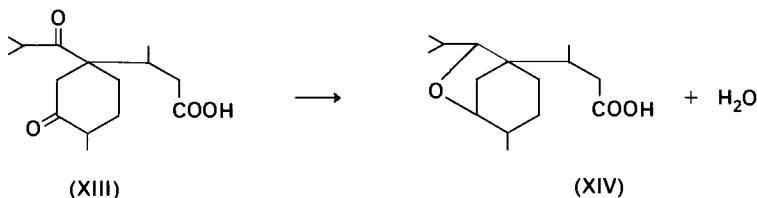
products obtained in reduction of cohulupone (XV) depended markedly on the catalyst used. Cohulupone, reduced over palladium chloride in methanol, gave a mixture of XVI and XVII. Hydrogenation over platinum oxide in methanol gave only 1% of XVII and principally XVI; with acetic acid 25% of XVII was obtained. Hydrogenation of cohulupone over palladium-on-barium sulfate gave XVII in 87% yield. No condition was found under which cohulupone could be reduced to tetrahydrocohulupone directly (Burton and Stevens, 1963; Burton et al., 1964).

(XVI)   (XV)   (XVII)
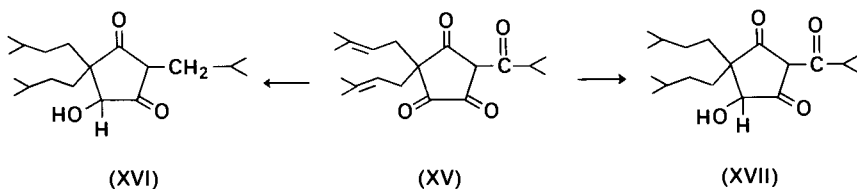
Outstanding results were obtained, in reduction of tetramethyl-1,3-cyclobutanedione to the corresponding diols, over 5% ruthenium-on-carbon in methanol at 125°C and 1000–1500 psi. The hydrogenation proceeded rapidly with no detectable formation of by-products. A pure product was obtained by removal of the catalyst and evaporation of the solvent.

Palladium, platinum, and rhodium catalysts gave poor results (Hasek *et al.*, 1961).
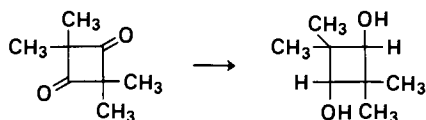
Selective hydrogenations of the cyclic diketones (XVIII and XIX) to the corresponding ketols were achieved over platinum oxide in acetic acid when hydrogen absorption was limited to one equivalent. The successful outcome of these hydrogenations is particularly interesting, in that attempts to produce the ketols by use of limited amounts of lithium aluminum hydride gave only diols and unchanged diketones (Blomquist and Wolinsky, 1955).

(XVIII) $n = 7$
(XIX) $n = 8$

(60%)

Hydrogenolysis

γ-Diketones readily undergo hydrogenolysis on reduction and form tetrahydrofurans, as noted earlier. Cyclization and hydrogenolysis may also occur with δ-diketones, affording tetrahydropyrans and, through aldolization reactions, cyclohexanone derivatives. Hydrogenation of 2,6-heptanedione over platinum-on-carbon at 200°C in cyclohexane solvent gave a mixture of 40% 2,6-dimethyltetrahydropyran, 43% 3-methylcyclohexanone, and 15% 3-methylcyclohexanol (Shuikin and Vasilevskaya, 1964):
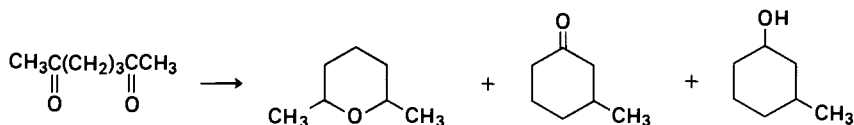
β-Diketones also undergo hydrogenolysis under mild conditions. The facile loss of water from β-diketones suggests that hydrogenolysis may occur through an enol form. Hydrogenation of 2-acetylcyclohexane-1,3-dione (XX) over 30% palladium-on-carbon in ethanol gave mainly 2-acetylcyclohexanone (XXI) and, in ethanol containing one equivalent of sodium hydroxide to promote enolization, a mixture of 2-ethylcyclohexane-1,3-dione (XXII) (45%) and 2-acetylcyclohexanone (Smith, 1953).

(XXI)   (XX)   (XXII)   + XXI
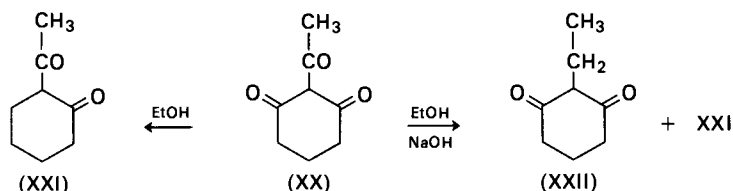
Dehydroacetic acid (XXIII) was selectively reduced over 10% palladium-on-carbon in ethyl acetate at 80°C to afford XXIV in 56% yield:

(XXIII)   (XXIV)
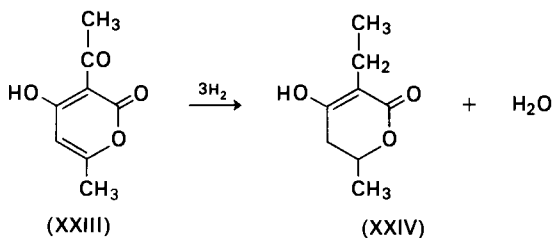
Similarly, veratrylidenedehydroacetic acid (XXV) afforded XXVI. This reduction was best carried out in two stages. Improved yields were obtained in the first stage when recovered catalyst was used instead of new catalyst (Walker, 1956).

(XXV)
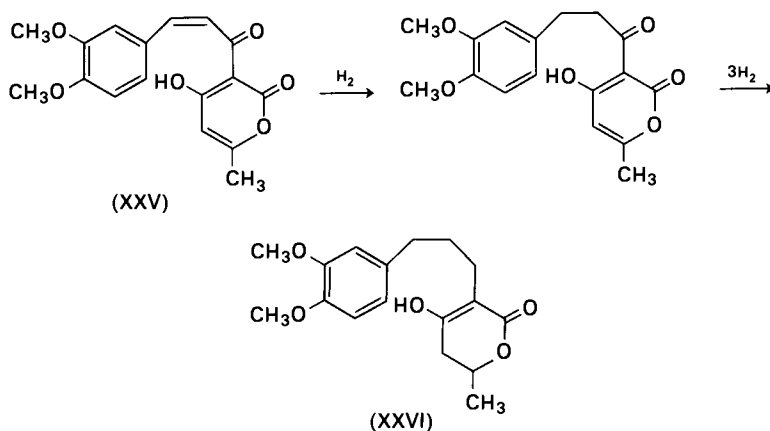
(XXVI)

   a. *Solvent.* The course of reduction of 1,3-diketones seems to be unusually sensitive to solvent. Hydrogenation of dimedone (XXVII) over a mixture of platinum-on-carbon and chloroplatinic acid gave a mixture of 1,1-dimethyl-cyclohexane (XXVIII) and 3,3-dimethylcyclohexanol (XXIX) in ratios that depended on the solvent.The yields of XXVIII and XXIX were, in acetic acid, 17 and 65%, respectively; in diethyl ether 19 and 46%, in dioxane 10 and 40%, and in water 0 and 100% (Liberman and Kazanskii, 1946). The

mixture of platinum-on-carbon and chloroplatinic acid was found to be more effective than platinum-on-carbon alone. The particularly high activity for this mixed catalyst may be due to platinum-on-carbon catalyzing the reduction of chloroplatinic acid by hydrogen to a very finely divided platinum (Patrikeev and Liberman, 1948).

(XXVII)   (XXVIII)   (XXIX)
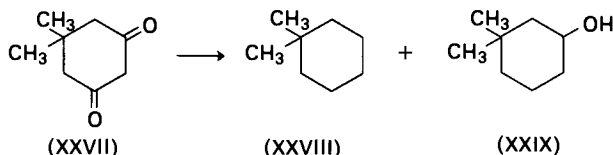
Similarly the unsaturated 1,3-diketone, cyclopentene-3,5-dione, underwent extensive hydrogenolysis on reduction over platinum oxide in ethyl acetate. About 2.7 molar equivalents of hydrogen were absorbed at essentially constant rate, resulting in roughly equal amounts of cyclopentanone and β-hydroxycyclopentanone. The authors suggested that the hydrogenation and hydrogenolysis of the carbonyl precede saturation of the carbon–carbon double bond, the assumption being that hydrogenolysis occurs through an allylic alcohol intermediate (DePuy and Zaweski, 1959). However, as noted above in dimedone hydrogenation, unsaturation is not a requisite for extensive hydrogenolysis of 1,3-diketones.
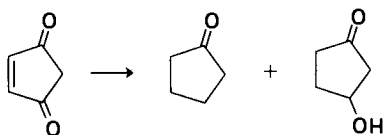
Hydrogenation of 3-methylcyclopentane-1,2,4-trione (XXX) over platinum oxide gave a mixture of products, in proportions that varied with the solvent. Hydrogenation of XXX in ethyl acetate afforded 4-hydroxy-2-methylcyclopentane-1,3-dione (XXXI) in 62 % yield. In ethanol the yield of XXXI dropped to 39 %, and 15 % of the hydrogenolysis product, 2-methylcyclopentane-1,3-dione (XXXII), was also obtained. In acetic acid solvent still more hydrogenolysis occurred, and in water was extensive (Orchin and Butz, 1943). The hydroxy diketone was shown not to be an intermediate in the formation of XXXII.

(XXX)   (XXXI)   (XXXII)
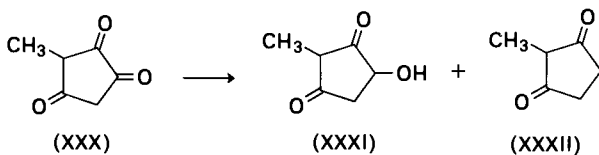
b. Amount of Catalyst. Hydrogenolysis may be controlled to some extent by the amount of catalyst used. Reduction of methyl 3,6-diketo-12α-acetoxyetioallocholanate over a small amount of platinum oxide in acetic acid gave

a low yield of the deoxy derivative, methyl 6β-hydroxy-12α-acetoxyetioallo-cholanate, but the yield could be raised to 38% when a larger amount of catalyst was used. A good yield of the dihydroxy compound was obtained by first using a small amount of catalyst and then, after absorption of one mole of hydrogen was complete, adding more catalyst (Jeanloz et al., 1947).

D. UNSATURATED ALIPHATIC KETONES

Unsaturated aliphatic ketones may be reduced at either or both points of unsaturation, the products of reduction being determined in great measure by the substrate itself. The present discussion is limited to reductions in which at least the carbonyl function is reduced (further discussion of this type of compound is given in the chapter on olefins, where reductions in which at least the olefin is reduced are emphasized).

Generally hydrogenation of an unsaturated aliphatic ketone proceeds with preferential saturation of the olefinic function. For instance, mesityl oxide was reduced over 5% palladium-, platinum-, rhodium-, and ruthenium-on-carbon in various solvents, and in every case the reduction was highly selective; after absorption of one equivalent of hydrogen, only methyl isobutyl ketone was found. If the reduction were allowed to continue, the ketonic function was also reduced at a moderate rate over platinum, rhodium, or ruthenium catalysts, but very slowly, if at all, over palladium (Breitner et al., 1959). Similarly, catalytic hydrogenation of 2-benzylidenecyclopen-tanone over palladium-on-carbon absorbed only one mole of hydrogen to give 2-benzylcyclopentanone in high yield. But reduction over platinum oxide in methanol absorbed 160% of one mole to give 2-benzylcyclopen-tanone in 70% yield and 2-benzylcyclopentanol in 15-20% yield. With platinum oxide in methanol-hydrochloric acid a little over two moles of hydrogen were absorbed to give 30-40% of 2-benzylcyclopentanone, 5% of cis-2-benzylcyclopentanol, and 40-50% of a material that was presumably benzylcyclopentane. The authors attributed the various results to changing ratios of 1,2-, 3,4-, or 1,4-addition (Phillips and Mentha, 1956).

Catalytic hydrogenation of unsaturated ketones does not always result in preferential reduction of the double bond, and various structural features may cause the reduction to be nonselective or even permit preferential hydrogenation of the ketone group. The relatively unhindered ketonic function in ethyl 2,3-dimethyl-5-carbethoxy-6-one-2-heptenoate was reduced over platinum oxide in ethanol in preference to the highly hindered tetra-substituted double bond (Adams and Gianturco, 1957). Hydrogenation of XXXIII over 10% palladium-on-carbon in ethanol resulted in loss of the ketonic oxygen with retention of the carbon–carbon double bond to afford XXXIV. The N-methyl derivative behaved similarly. Over Raney nickel at

170–205°C a 48 % yield of XXXV was obtained together with 6 % of XXXIV (Koelsch and Ostercamp, 1961).

(XXXV)   (XXXIII)   (XXXIV)
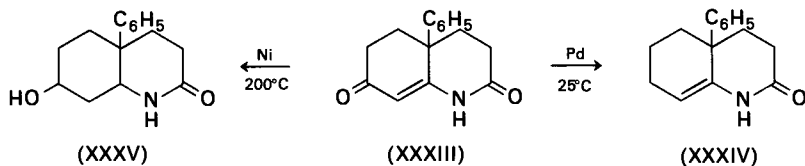
Reduction of the unsaturated ketone (XXXVI), which bears a structural resemblance to XXXIII, proceeded with saturation of both functions over palladium-on-carbon in acetic acid or over platinum oxide in ethanol to afford XXXVII. Reduction of XXXVI over Raney nickel in ethanol at 110°C was highly exothermic, and gave a rearranged product (XXXVIII) in which a molecule of solvent was incorporated. Formation of XXXVIII involves saturation of the double bond and ethylation of the nitrogen atom by the solvent, hydrogenolysis of a carbon-nitrogen bond β to both a carbonyl and a carbethoxy group, cyclization of the amine and ester groups, and reduction of the ketone function (Albertson, 1952). Alkylation of basic nitrogen by an alcohol solvent is not uncommon in reductions over Raney nickel (Freifelder and Stone, 1961).

(XXXVIII)   (XXXVI)   (XXXVII)
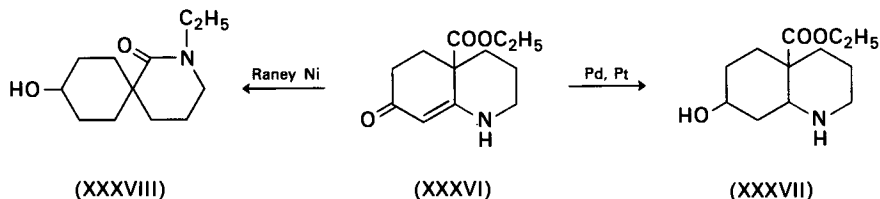
Catalytic hydrogenation of XXXIX over platinum oxide in ethanol gave the unsaturated hydroxy ester (XL) and, in acetic acid, the lactone of the saturated alcohol (XLI). The former reduction was not readily reproducible (Meyer and Levinson, 1963).

(XL)   (XXXIX)   (XLI)
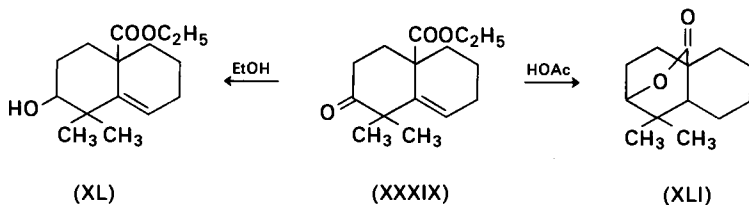
Preferential reduction of the ketone group in unsaturated ketones has occurred also over ruthenium, a metal that, because of its high activity in reduction of carbonyl functions and low activity in reduction of olefins,

might be expected to be the most suited among the platinum metals for selective reductions in this sense. There are, however, insufficient data available to demonstrate the correctness of this proposition. The adduct of 1-acetoxy-1,3-butadiene and benzoquinone (XLII) absorbed exactly three equivalents of hydrogen over ruthenium-on-carbon in methanol, and the dihydro adduct (XLIII) absorbed exactly two equivalents. The authors concluded from these data that the olefinic bond and the carbonyl in the enedione system were reduced, whereas the isolated double bond was not. The course of this reduction was different over palladium; the olefinic linkages were saturated without reduction of the carbonyls (Kaye and Matthews, 1964).
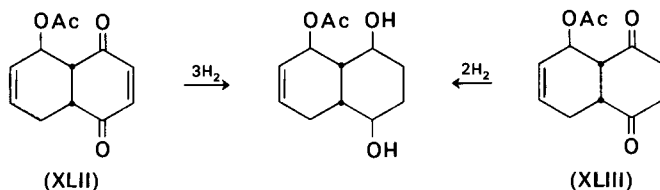
Aromatization

Ketones that are part of a potential aromatic system may be converted to phenols on catalytic hydrogenation. Reduction of a benzisoxazolone (XLIV) over platinum oxide in acetic acid–acetic anhydride resulted in aromatization and acetylation to afford XLV. By a more prolonged reduction over 10% palladium-on-carbon the substrate underwent hydrogenolysis as well (XLVI) (Buchanan *et al.*, 1963a).
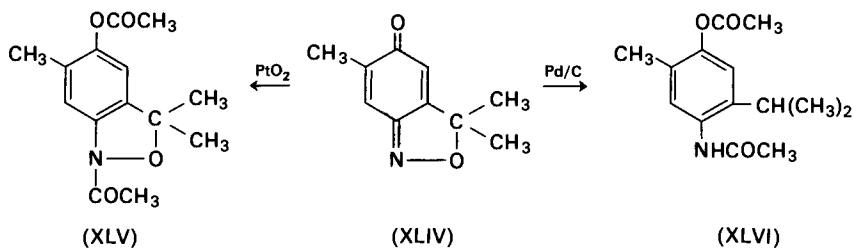
Aromatization may be accompanied by dealkylation, as in the reduction of humulone (XLVII) to a mixture of tetrahydrohumulone (XLVIII) and humulohydroquinone (XLIX). The percentage of humulohydroquinone is greatest at low pH and falls as the pH rises. A linear relation between log (percent humulohydroquinone) and $-k$pH held for all catalysts tested (platinum oxide, palladium-on-carbon, palladium-on-strontium carbonate, and rhodium-on-alumina). At any pH the percentage of humulohydroquinone

was greatest when palladium catalysts were used (Anteunis and Verzele, 1959).

(XLVII)   (XLIX)   (XLVIII)
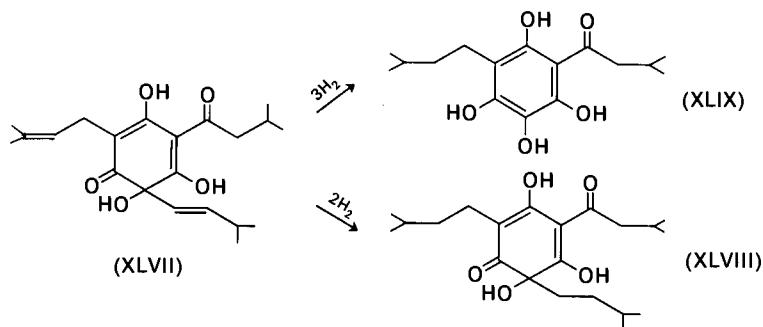
E. TRANSANNULAR REACTIONS

Hydrogenation of certain cyclic diketones may proceed with ring closure either through transannular aldolization or by establishment of a new carbon–carbon bond through interaction of both carbonyl functions. For instance, catalytic hydrogenation of cis-cyclonon-3-ene-1,6-dione, (L) over 10% palladium-on-carbon in ethanol was accompanied by transannular aldolization of the expected cyclononane-1,5-dione to form tetrahydro-indanone (LI) (Buchanan et al., 1963b).

(L)   (LI)
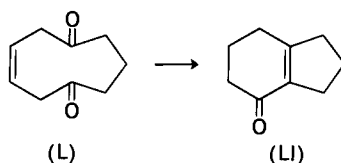
Catalytic hydrogenation of the cyclooctane-1,5-dione (LII) over nickel in dioxane afforded the cis-glycol (LIII) in 68% yield through bridging of the carbonyl functions (Cope and Kagan, 1958).

(LII)   (LIII)
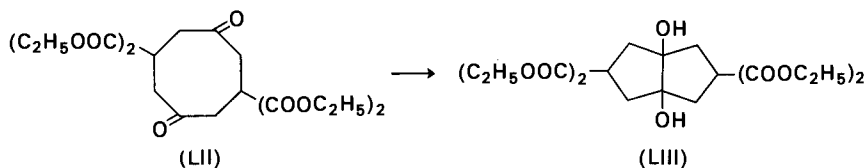
II. AROMATIC KETONES

Aromatic ketones can be reduced to either the corresponding alcohol or hydrocarbon with little difficulty. The alcohol is usually an intermediate in

the reduction, and can be obtained in good yield if the reduction is interrupted after theoretical absorption of hydrogen. In many reductions, hydrogen absorption slows markedly after formation of the alcohol. It has been reported (Hartung and Crossley, 1934) that propiophenone was reduced directly over palladium-on-carbon in ethanol to propylbenzene; when the reduction was interrupted before completion, only starting material and propylbenzene were found with no trace of phenylethylcarbinol. This unusual result was later attributed (Meschke and Hartung, 1960) to impurities in the catalyst (Hartung and Chang, 1952). Subsequent work with catalysts then at hand showed the reduction to propylbenzene to proceed through an intermediate carbinol.

A. HYDROGENOLYSIS

Hydrogenolysis of a ketone group adjacent to an aromatic nucleus occurs readily. The reduction usually proceeds through an intermediate carbinol, and a sharp decline in rate is frequently observed after the carbinol stage has been reached. Hartung and Simonoff (1953) tabulated forty-seven hydrogenolysis reactions of aromatic ketones over palladium-on-carbon, palladium-on-barium sulfate, or palladium black. The yields were generally high and the conditions mild. Methanol, ethanol, acetic acid, ethyl acetate, acetic acid–perchloric acid, and acetic acid–sulfuric acid were used as solvents. When the ketone is complex, high catalyst loading levels may be necessary to obtain satisfactory results. Hydrogenolysis of the hindered ketone, N-carbethoxy-2-(2-acetyl-3,4,5-trimethoxyphenyl)ethylamine, was achieved over 10% palladium-on-carbon in acetic acid at 80°C with equal weights of catalyst and substrate (Karady, 1962).

1. Temperature

Elevated temperatures promote hydrogenolysis. Walker (1956) reduced o-hydroxyacetophenone to 2-ethylphenol in 78% yield over 10% palladium-on-carbon at 40 psig and 80°C, refuting an earlier generality that reduction to the hydrocarbon does not take place in aryl alkyl ketones that contain a phenolic hydroxyl in the ortho position (Hartung and Simonoff, 1953). At 60°C and 40–20 psig, γ-(3,4,5-trimethoxybenzoyl)butyric acid suffered hydrogenolysis over 5% palladium-on-carbon, affording the deoxy compound in 90% yield (Koo, 1953). The product from the catalytic reduction of the keto acid (LIV) over 10% palladium-on-carbon in ethyl acetate depended on the temperature. At 25°C the hydroxy acid (LV) was formed, and at 80°C a quantitative yield of the deoxy compound (LVI), which perhaps arose through interaction of the ketone and carboxyl groups (Walker, 1958).
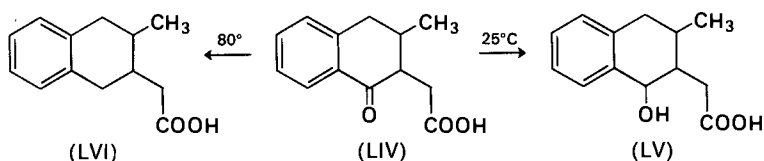
2. Catalysts

Palladium is generally the most useful of the platinum metal catalysts for hydrogenolysis of aromatic ketones, in that it combines a good activity for hydrogenation and hydrogenolysis of the ketone with low activity for hydrogenation of the aromatic ring. For example, p,p'-dihydroxydiphenyl-methane was isolated in 95% yield from reduction of p,p'-dihydroxybenzo-phenone over 5% palladium-on-carbon, whereas under similar conditions a platinum catalyst caused ring reduction (Levine and Temin, 1957). However, reduction of the aromatic ring may occur in certain compounds even over palladium if the reduction is allowed to continue too long. Hydrogenation of o-dibenzoylbenzene in ethanol over 5% palladium-on-carbon afforded o-dibenzylbenzene in 66% yield; if the reduction were allowed to continue a slow ring saturation ensued (Jensen, 1960).

B. REDUCTION TO THE CARBINOL

Reduction of aromatic ketones to the corresponding carbinol usually occurs readily. Further hydrogenation may be prevented by interrupting the reduction after theoretical absorption of hydrogen, but in many hydro-genations, especially of complex molecules, the reduction virtually ceases after formation of the carbinol. If hydrogenolysis occurs, it may be minimized by deactivation of the catalyst by organic bases (Kindler et al., 1957). Re-duction of LVII over a 20% palladium-on-carbon catalyst (Hiskey and Northrop, 1961), poisoned with nicotinamide or N,N-diethylnicotinamide, afforded LVIII in 63% yield. Reduction under standard conditions (un-specified) gave primarily the hydrogenolysis product (Werbel et al., 1964). Excellent yields of carbinols have been obtained by using aqueous ammonia as a solvent (Cohen et al., 1963).
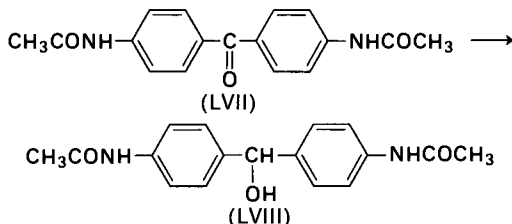
Aromatic α-diketones may be reduced stepwise with reduction to the alcohol of first one carbonyl and then the other, followed by hydrogenolysis of first one alcohol and then the other. A complete series of compounds was prepared in this way from anisil in excellent yield over platinum oxide. The solvent has an important effect on this reduction; anisil was reduced best in ethyl acetate, benzil in ethanol, and piperil could be reduced only in pyridine (Buck and Jenkins, 1929).

1. Catalysts

Palladium is the most used of the platinum metals for hydrogenation of aromatic ketones to either the corresponding carbinol or hydrocarbon. Rhodium, ruthenium, and especially platinum have been used also, but concomitant or subsequent reduction of the aromatic ring may occur over these catalysts. Rhodium catalysts are in fact very useful for saturation of the aromatic nucleus with preservation of the oxygen (Kaye and Matthews, 1963). Platinum catalysts also have proved useful for preparing ring-saturated alcohols. Linstead and Levine (1942) reduced 9,10-phenanthra-quinone (LIX) to the saturated diol (LX) over platinum oxide in acetic acid.

(LIX)   (LX)
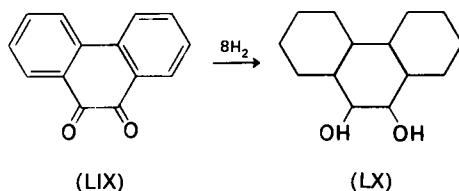
Excellent yields of aromatic carbinols have been obtained by reduction of aromatic ketones over platinum oxide (Mosettig and van de Kamp, 1933; Lyle et al., 1959), even with compounds where other catalysts failed (Smith and Holmes, 1951).

Several comparisons of catalysts for hydrogenation of aromatic ketones have been made. Acetophenone was reduced over 5% palladium-, platinum-, rhodium-, and ruthenium-on-carbon in several solvents. Palladium was generally the most active but the rates varied widely with the solvent and, in aqueous media, with the pH. There was no evidence of ring saturation over palladium (Breitner et al., 1959). In another study, acetophenone was reduced at low pressure over platinum oxide, 5% palladium-on-carbon, 5% rhodium-on-alumina, Raney nickel, and G-69 nickel. The reductions, carried out in ethanol, were interrupted after absorption of one equivalent of hydrogen, and the products examined by gas chromatography. Except over rhodium, where considerable ring hydrogenation occurred, the yields of 1-phenylethanol were high. Over 5% palladium-on-carbon, the catalyst of choice, the yield was 99.9% (Freifelder et al., 1964).

A most interesting study has been made of the effect of catalyst in hydrogenation of the isomeric acetylpyridines (Freifelder, 1964). Reduction of 2-acetylpyridine over 5% palladium-on-carbon gave good yields of 2-(1-hydroxyethyl)pyridine. Reduction over rhodium-on-carbon or platinum oxide gave mixtures that contained some ring-saturated material, as was expected.
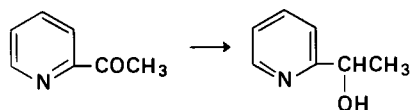
Mixtures were always obtained after absorption of one equivalent of hydrogen in reductions of 3-acetylpyridine over 5% palladium-on-carbon, 5% rhodium-on-alumina, or platinum oxide in water or ethanol. The mixture consisted of unchanged starting material, 3-(1-hydroxyethyl)-pyridine, and 3-acetyl-1,4,5,6-tetrahydropyridine. Over 5% palladium-on-carbon in ethanol the last material was 40% of the total product. Reduction
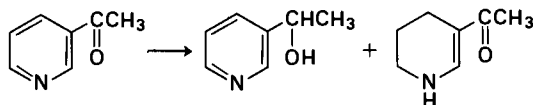
of 4-acetylpyridine followed still a different course to give a pinacol. Over palladium-on-carbon or rhodium-on-alumina the pinacol was obtained in 60% yield. Platinum oxide in water, on the other hand, gave much less pinacol and 4-(1-hydroxyethyl)pyridine was obtained in 78–80% yield. Other workers reduced 4-acetylpyridine over palladium oxide in absolute ethanol and obtained 4-(1-hydroxyethyl) pyridine in 50–57% yield. Pinacol formation was not reported (Nielsen *et al.*, 1964).
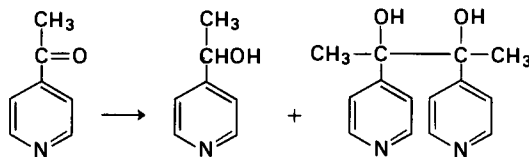
2. Acidic and Basic Media

Small amounts of strong acid may have a marked effect on hydrogenation of aromatic ketones, particularly insofar as acid promotes hydrogenolysis of the intermediate carbinol to the deoxy compound. For instance, reduction of a methyl benzohydrindonepropionate over platinum oxide in alcohol ceased after absorption of one mole of hydrogen to give methyl perinaphthindan-1-ol-6-propionate, but if a few drops of sulfuric acid were then

added another mole was rapidly absorbed to give methyl 6-perinaphthin-danpropionate (Lock and Walter, 1944). Similarly, hydrogenolysis of the keto function in LXI over 10 % palladium-on-carbon in ethanol was markedly accelerated by addition of a small amount of sulfuric acid. Both the Clemmensen and Huang-Minlon reductions failed to give good results with this compound (Wilt and Schneider, 1961).

(LXI)
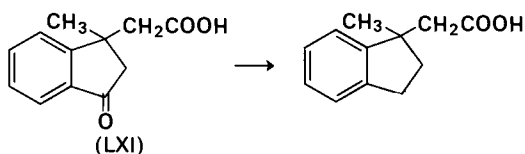
On the other hand, trace quantities of acid proved detrimental in reduction of ω-fluoroacetophenone to 1-phenyl-2-fluorethanol over palladium-on-carbon. High yields could be obtained only if the starting material were carefully purified and acid-free. If acid were present, hydrogenation did not stop after one equivalent of hydrogen was absorbed and considerable amounts of dehalogenated products were formed (Bergmann and Kalmus, 1954).

Acid may also promote ring saturation (Theilacker and Drössler, 1954). Acetophenone, reduced over a reused platinum oxide in dioxane, afforded phenylethanol in 100% yield, but in the presence of only 0.3% acetic acid the product was a mixture of phenylethanol, ethylbenzene, ethylcyclohexane, and cyclohexylethanol. From these and a number of other experiments, the authors suggested that two pathways for reduction of acetophenone exist. One pathway consists of the successive steps, acetophenone ——→ phenylethanol ——→ ethylbenzene ——→ ethylcyclohexane. The second route is the direct reduction of acetophenone to α-cyclohexylethanol, involving reduction of the benzene ring prior to or concomitant with reduction of the carbonyl. Both paths are activated by acids. The first path is strongly inhibited by base whereas the second path is insensitive to inhibition by base. Sodium hydroxide inhibits reduction of acetophenone over palladium oxide (Theilacker and Drössler, 1954) and over palladium-on-carbon (Breitner et al., 1959). Acid may also accelerate hydrogenolysis relative to reduction of other functions in the molecule. Reduction over palladium black of a series of 4-halo-2-acyl phenols to the corresponding alkyl phenols was accompanied by extensive dehalogenation. The loss of halogen could be kept to low levels by use of small amounts of perchloric acid or preferably sulfuric acid to increase the rate of hydrogenolysis relative to the rate of dehalogenation (Kindler et al., 1953). Similarly, by use of strong acid to promote hydrogenolysis, the complex unsaturated aromatic ketone (LXII) could be converted to the deoxy compound (LXIII) with preservation of the carbon–carbon double bond (Johnson et al., 1957). The hydrogenolysis of 0.93 gm LXII was carried out

in 30 ml glacial acetic acid containing 0.2 ml 60% perchloric acid (Rosenmund *et al.*, 1942) over 0.2 gm 30% palladium-on-carbon catalyst (Linstead and Thomas, 1940), and required 80 minutes for absorption of two equivalents. Hydrogenation of LXII over 30% palladium-on-strontium carbonate in ethyl acetate afforded, after absorption of two equivalents, the saturated alcohol (LXIV).
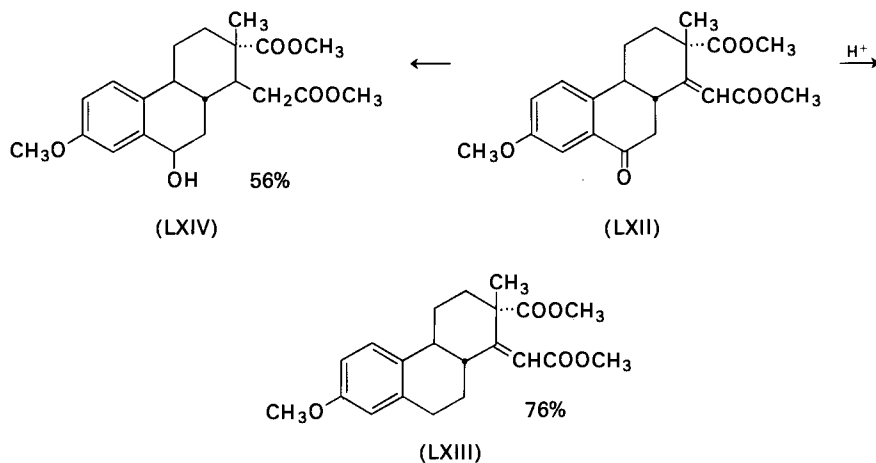
In certain reductions the acid had best be added after the alcohol stage is reached. Reduction of a Mannich base (LXV) to the corresponding amino alcohol over platinum oxide was accomplished in an acidic buffer of ammonium acetate–acetic acid. Strong acid at this stage led to decomposition of the substrate. The reduction was stereoselective and gave a 72% yield of the β-phenanthrol (LXVI). Further reduction over palladium-on-carbon in acetic acid–hydrochloric acid readily gave the corresponding deoxy compound (LXVII) (Murphy, 1961).
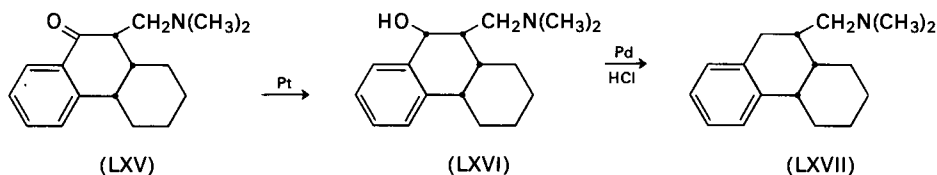
Alkaline solutions have sometimes proved useful in promoting hydrogenolysis by preventing formation of compounds not easily amenable to further reduction. Catalytic hydrogenation of *o*-acetylbenzoic acid over Raney nickel did not proceed beyond the hydroxy stage, which then cyclized to the lactone (Huisgen and Rauenbusch, 1961). However, reduction of

o-acetylbenzoic acid in the form of its sodium salt in water over 5 % palladium-on-carbon at 80°C afforded 2-ethylbenzoic acid (Kollonitsch *et al.*, 1962).
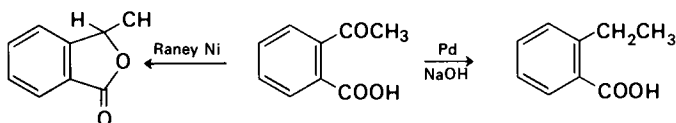
3. Amino Ketones

Amino ketones have been reduced to the corresponding amino carbinols both as amine salts and as the free base. Excellent yields (Bolhofer, 1952, 1953; Hornbaker and Burger, 1955; Müller *et al.*, 1958; Rebstock *et al.*, 1951) are frequently obtained, perhaps because of inhibition of hydrogenolysis by the amine (Kindler *et al.*, 1951). Whether the free base or a salt should be used may depend on only minor structural variations in the substrate. For instance, 3-alkylamino-4-keto-1,2,3,4-tetrahydrophenanthrene hydrochlorides were reduced to the corresponding amino alcohols over platinum oxide without complication. However, reductions of 1-keto-2-alkylamino-1,2,3,4-tetra-hydrophenanthrene hydrochlorides were very erratic. Satisfactory results were obtained consistently by reduction of the free base in methanol (Mosettig and Burger, 1935). Apparently the free amine inhibited over-hydrogenation.
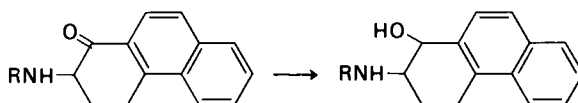
Inhibition of hydrogenation by the basic nitrogen atom is apt to accentuate the effect of solvent on the course of reduction. Hydrogenation of LXVIII over 10% palladium-on-carbon in water afforded the carbinol (LXIX), but in ethanol only hydrogenolysis of the benzyl group occurred; the reduction ceased spontaneously after absorption of one equivalent (Vaughan and Blodinger, 1955).
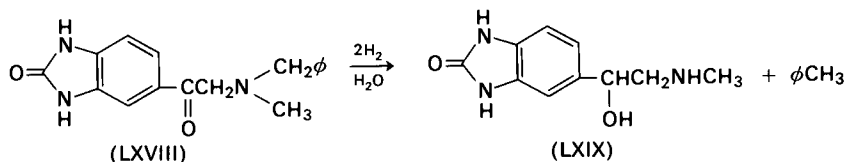
Difficult reductions of hindered aromatic amino ketones can be promoted by small amounts of strong acid. Catalytic reduction of 1 gm LXX in 20 ml acetic acid containing 2 ml 72% perchloric acid was carried out over 0.4 gm 5% palladium-on-barium sulfate at 70°C. In 20 hours only one equivalent of hydrogen had been absorbed. Hydrogenolysis of the oxygen function was

negligible, as the carbinol (LXXI) was isolated in 90% yield (Stevens and Chang, 1962).

(LXX)   (LXXI)
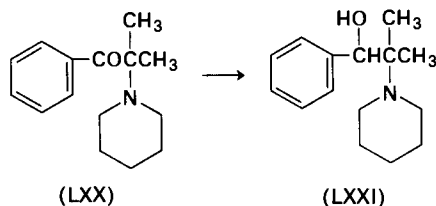
Diazo Ketones. Birkofer (1947) has discussed at length the hydrogenation of diazo ketones. Depending on the catalyst, solvent, and substrate, the reduction yields varying amounts of pyrazines, amino ketones, diketones, amino alcohols, and hydrazones. In general, when R in N_2CHCOR is aliphatic or alicyclic, hydrogenation gives chiefly the hydrazone; when R is phenyl or benzyl, one nitrogen atom is lost as ammonia, and the amino ketone, which may undergo further transformations, is formed. In the presence of copper oxide or hydrogen chloride, both nitrogen atoms are lost and methyl ketones and 1,4-diketones are formed.

C. UNSATURATED KETONES

The reduction of unsaturated ketones is discussed in the chapter on hydrogenation of olefins, where reactions in which at least the olefin is reduced are emphasized. Reduction of both functions presents no special complication, except in certain compounds where interaction occurs (Kreutzberger and Kalter, 1960). Preferential reduction of the carbon–carbon double bond is more easily accomplished than preferential reduction of the ketone, which requires some special technique. For instance, unsaturated alcohols are formed by hydrogenation of benzalacetone and chalcone over colloidal palladium promoted by ferrous sulfate and zinc acetate* (Csuros *et al.*, 1946).

R = —CH$_3$, —C$_6$H$_5$
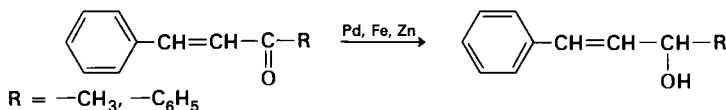
Overhydrogenation of aromatic ketones over platinum oxide may be prevented by addition of ferrous or ferric chloride. Without iron, *p*-methylchalcone smoothly absorbed 9 moles of hydrogen to afford the perhydro compound; with the appropriate amount of additive, the reduction stopped

* In contrast to this result, cinnamaldehyde reduced over palladium-zinc-iron catalysts gave the saturated aldehyde; the unsaturated alcohol could be obtained only over promoted platinum catalyst (Rylander *et al.*, 1963).

spontaneously after absorption of 2 moles and gave only the saturated carbinol (Weygand and Werner, 1938).

Reduction of chalcone over platinum oxide in ethanol, made alkaline to litmus with potassium hydroxide, stopped after absorption of one mole of hydrogen to give the saturated ketone; in ethanol, made acid with a few drops of hydrochloric acid, three moles of hydrogen were absorbed at constant rate to give 1,3-diphenylpropane. On the basis of this and other experiments, Weidlich and Meyer-Delius (1941) proposed a rule that the products of hydrogenation in acid medium arise from 1,2-addition at the carbon–carbon or carbon–oxygen double bond, and those in alkaline medium from 1,4-addition to the conjugated system. Later workers proposed essentially the opposite, namely, that in acid medium a 1,4-addition, and not a 1,2-addition, occurs. The effect of base was undefined (Augustine and Broom, 1960).

Olefins conjugated with a carbonyl function seem to be reduced, perhaps by 1,4-addition, with unusual ease, even when the olefin is tetrasubstituted. Shriner and Anderson (1939) reduced LXXII to the isopropyl derivative (LXXIII) over platinum oxide in ethanol, and to LXXIV over palladium-on-carbon in ethanol. The olefin was reduced in a few minutes whereas the ketone required 24 hours.
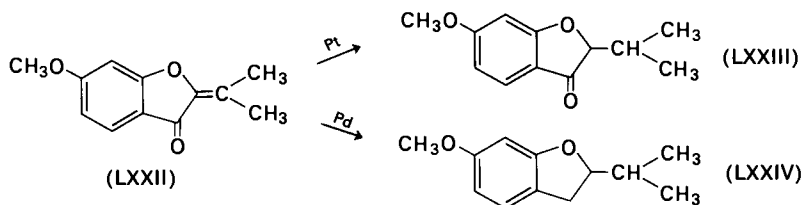
Tetracyclone (LXXV) was hydrogenated over 10% by weight of platinum black in acetic acid until the color was discharged and afforded LXXVI in 73% yield. Reduction over 500% by weight of platinum oxide in acetic acid afforded tetraphenylcyclopentane (LXXVII) in 85% yield (Sonntag et al., 1953).
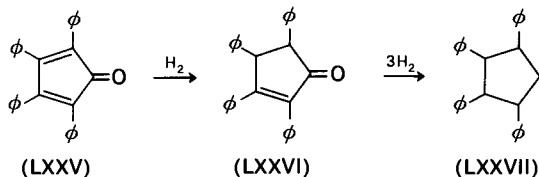
A surprising generation of a nitro function has been observed during hydrogenation of an aromatic ketone containing an isoxazoline oxide system (LXXVIII). This nitro product (LXXIX) was obtained in only 5% yield. The major products (LXXX), themselves unexpected, were stereoisomeric carbinols, formed with the isoxazoline system still intact. Evidently

the carbonyl group is reduced more readily than any part of the $\begin{matrix} \diagdown \\ \diagup \end{matrix} C{=}N \begin{matrix} \diagup O \\ \diagdown O \end{matrix}$

system (Kohler and Davis, 1930).

$$
\text{(LXXVIII)} \quad
\begin{array}{c}
C_6H_5{-}CH{-}CH{-}C{-}C_6H_4OCH_3 \\
| \qquad \diagdown \; \underset{O}{\overset{O}{||}} \\
C_6H_5{-}C{=}N \\
\diagdown \\
O
\end{array}
$$

$$
C_6H_5{-}CH{-}CH{-}CH{-}C_6H_4OCH_3 \qquad
\begin{array}{c}
C_6H_5{-}CH{-}CH_2{-}C{-}C_6H_4OCH_3 \\
| \qquad\qquad\quad || \\
C_6H_5{-}CHNO_2 \qquad O
\end{array}
$$

$$
\begin{array}{c}
| \qquad \diagdown \; | \\
\; \qquad O \; OH \\
C_6H_5{-}C{=}N \\
\diagdown \\
O
\end{array}
$$

(LXXX)   (LXXIX)
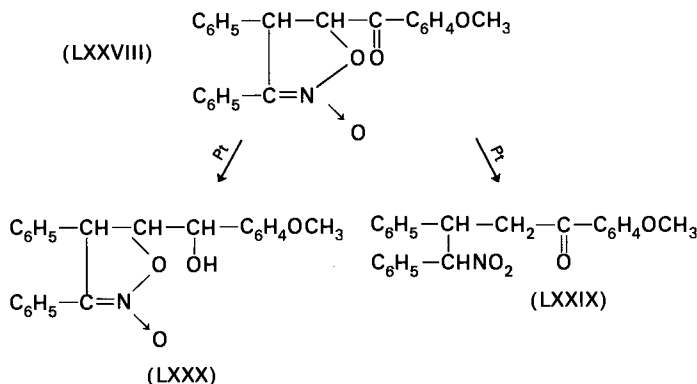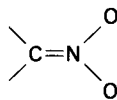
III. STEREOCHEMISTRY

An often used rule, based on extensive studies by Skita in the 1920's, is that reduction in acid solvents leads to products rich in *cis* isomer, and in neutral or alkaline solvents to products rich in *trans* isomer. Wicker (1956) has discussed this rule at some length and finds it to be misleading. The application of the rule is complicated by the fact that alkali in the presence of a hydrogenation catalyst can promote a ready isomerization of products, at least in some systems. For instance, *trans*-3,5,5-trimethylcyclohexanol was not isomerized in the presence of sodium carbonate without a catalyst present, nor over acid-washed platinum oxide, but was readily isomerized when a little sodium carbonate was added. Wicker also pointed out in discussing reduction of cyclohexanones that alkali and acid will affect the proportions of enol and keto forms. He concluded that prediction of the stereoisomeric composition of the products of catalytic hydrogenation is impossible, unless the conformational and tautomeric composition of the ketone is known (and perhaps not even then).

The von Auwers–Skita rules have been restated by Barton (1953) in more modern terms. A generalization applicable to steroids is that catalytic hydrogenation of both hindered and unhindered ketones in strongly acid media (rapid hydrogenation) affords the polar alcohols. Reduction in neutral media (slow hydrogenation) gives the equatorial alcohol if the ketone group is not hindered, the polar alcohol if it is strongly hindered.

Just how far these generalities may be extended is uncertain. This proposition has been discussed at some length by Findlay (1959), who pointed out a number of exceptions. He suggested that, especially with molecules

containing two or more basic atoms, the tendency of a ring to assume a particular conformation, and thus to yield a particular configuration of an attached substituent, is outweighed by the tendency of the molecule to assume a preferred orientation with respect to the catalyst through the coordinating power of the metal for the basic atoms. When this "anchor effect" is present it may make predictions based on steric considerations quite misleading. The unsaturated ketone (LXXXI) or its ester was reduced over 10% palladium-on-carbon in ethanol to the saturated hydroxy acid (LXXXII), in which the carboxymethyl and hydroxy groups were disposed *trans* to each other. In discussing the stereochemistry of this reduction, the authors (House *et al.*, 1960) noted that from a study of molecular models they could form no distinct preference as to which side of the compound would be adsorbed on the catalyst surface. They suggested consequently that the steric course was controlled primarily by the preferential adsorption of the carboxyl group or the carbomethoxy group on the catalyst surface.
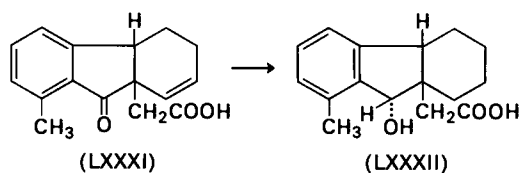
CATALYSTS

There are few reports in the literature comparing the performance of several platinum metal catalysts in hydrogenations leading to a mixture of stereoisomers, and reports comparing as many as four catalysts are rare indeed. Consequently it is difficult to make generalities as to what kind of catalyst favors each isomer, but it is worth noting, as some of the following examples show, that drastic changes in the isomer ratio may be brought about by an appropriate change in the catalyst.

The stereochemical consequences of catalytic hydrogenation of 1-, 2-, and 3-ketoquinolizidines over platinum oxide, 5% rhodium-on-carbon, 5% ruthenium-on-carbon, and 10% palladium-on-carbon in ethanol and aqueous hydrochloric acid have been reported (Rader *et al.*, 1964). In the ethanolic hydrogenations the percentage of the axial hydroxyl epimer always decreased in the order, ruthenium > platinum oxide > rhodium > palladium, and the percentage change is strikingly large. For instance, in reduction of 1-ketoquinolizidine the percentage of axial hydroxyl produced by the four catalysts was 71, 33, 26, and 7%, respectively. In acidic media no distinct overall correlations were evident. In this interesting paper the authors discussed the results at some length. They suggested that the unprotonated

bridgehead nitrogen influenced the stereochemistry by its ability to bond with the catalyst surface, and thus produce an "anchor effect." The effect of catalyst on the stereochemistry of the products cannot be divorced from the solvent used in the reduction. For instance, in reduction of 3-ketoquino-lizidine over 5% ruthenium-on-carbon, the percentage of axial hydroxyl epimer was 72% in ethanol and 86% in aqueous hydrochloric acid; the corresponding figures for reduction over 10% palladium-on-carbon were 3% and 82%.
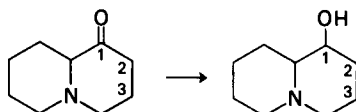
A consistent relationship of *cis-trans* isomer distribution was found in reduction of the methylcyclohexanones (Table III). Here the percentage of the more stable alcohol increased regularly in the series, 5% rhodium-on-carbon, 5% ruthenium-on-carbon, platinum oxide, and 5% platinum-on-carbon. For some unknown reason, hydrogenation of 2-methylcyclohexanone over rhodium proved very difficult, although this same sample was easily reduced over the other catalysts. The ready explanation that this particular sample contained a poison specific for rhodium proved false; when *o*-cresol was mixed with 2-methylcyclohexanone, reduction of the aromatic proceeded easily, leaving the ketone unchanged (Rylander and Steele, 1963). Hydrogenation of 2-methylcyclohexanone in acetic acid–hydrogen chloride over platinum black gave exclusively the *cis* isomer, but reduction in dioxane, acetic acid, butanol-sodium butoxide, cyclohexane, and butyl ether gave mixtures of *cis* and *trans* isomers. There was apparently no correlation between the rate of hydrogenation and the amount of *cis* isomer (Anziani and Cornubert, 1945). Other workers obtained a 91% yield of 2-methylcyclohexanol containing 93% of the *cis* isomer on reduction of 2-methylcyclohexanone over platinum black in acetic acid–hydrochloric acid; in

TABLE III

ISOMER DISTRIBUTION IN METHYLCYCLOHEXANOLS FROM HYDROGENATION
OF METHYLCYCLOHEXANONES[a]

Substrate	Percent more stable isomer			
	5% Rh/C (300 mg)	5% Ru/C (300 mg)	PtO$_2$ (500 mg)	5% Pt/C (300 mg)
2-Methylcyclohexanone	——	57	61	64 (*trans*)
3-Methylcyclohexanone	41	63	75	80 (*cis*)
4-Methylcyclohexanone	46	62	65	74 (*trans*)

[a] Temperature: 100°C; pressure 1000 psig.

acetic acid alone, an 88% yield of product containing 66% *cis* isomer was obtained (Hückel and Hubele, 1958). Yields of *cis* isomers of 48%, 50%, and 39%, respectively, were obtained by reduction of 2-, 3-, and 4-methyl-cyclohexanones over platinum oxide in acetic acid containing dry hydrogen chloride (Eliel and Lukach, 1957).

Temperature

There are few reports on the effect of temperature on the stereochemistry of hydrogenation. Most hydrogenations are conducted at room temperature and are usually heated only to increase the rate of reduction. The opportunity of changing the stereochemistry of the products by changing the temperature of reduction seems to have been largely overlooked.

Wicker (1957) has proposed several practical guides for controlling the proportions of isomers derived from phenols and cyclohexanones. To obtain preponderance of the more stable isomer, isomerization should be encouraged; the catalyst should be alkaline (preferably nickel) or when platinum oxide is used it should not have been acid-treated, and acidic solvents must not be used. The temperature should be as high as possible, and the reaction should be continued beyond the time hydrogen ceases to be absorbed to permit further isomerization. To obtain a preponderance of the less stable isomer, the temperature should be as low as practical. Isophorone, reduced at 130°C over nickel catalysts, gave about 70% of the more stable *cis*-3,3,5-trimethylcyclohexanol; at room temperature the product was 90% of the less stable *trans* isomer. Over this catalyst either isomer could be isomerized to a mixture of the two (Peppiatt and Wicker, 1955).

REFERENCES

Adams, R., and Gianturco, M., *J. Am. Chem. Soc.* **79**, 166 (1957).
Adams, R., Miyano, S., and Fles, D., *J. Am. Chem. Soc.* **82**, 1466 (1960).
Adams, R., Miyano, S., and Nair, M. D., *J. Am. Chem. Soc.* **83**, 3323 (1961).
Albertson, N. F., *J. Am. Chem. Soc.* **74**, 249 (1952).
Anteunis, M., and Verzele, M., *Bull. Soc. Chim. Belges* **68**, 476 (1959).
Anziani, P., and Cornubert, R., *Bull. Soc. Chim. France* **12**, 359 (1945).
Augustine, R. L., and Broom, A. D., *J. Org. Chem.* **25**, 802 (1960).
Barton, D. H. R., *J. Chem. Soc.* p. 1027 (1953).
Bergmann, F., and Kalmus, A., *J. Am. Chem. Soc.* **76**, 4137 (1954).
Birch, A. J., Hochstein, F. A., Quartey, J. A. K., and Turnbull, J. P., *J. Chem. Soc.* p. 2923 (1964).
Birkofer, L., *Chem. Ber.* **80**, 83 (1947).
Blomquist, A. T., and Wolinsky, J., *J. Am. Chem. Soc.* **77**, 5423 (1955).
Bolhofer, W. A., *J. Am. Chem. Soc.* **74**, 5459 (1952).
Bolhofer, W. A., *J. Am. Chem. Soc.* **75**, 4469 (1953).
Breitner, E., Roginski, E., and Rylander, P. N., *J. Org. Chem.* **24**, 1855 (1959).

Brewster, J. H., *J. Am. Chem. Soc.* **76**, 6361 (1954).
Buchanan, G. L., Raphael, R. A., and Still, I. W. J., *J. Chem. Soc.* p. 4372 (1963a).
Buchanan, G. L., Hamilton, J. G., and Raphael, R. A., *J. Chem. Soc.* p. 4606 (1963b).
Buck, J. S., and Jenkins, S. S., *J. Am. Chem. Soc.* **51**, 2163 (1929).
Burton, J. S., and Stevens, R., *J. Chem. Soc.* p. 4382 (1963).
Burton, J. S., Elvidge, J. A., and Stevens R., *J. Chem. Soc.* p. 3816 (1964).
Carothers, W. H., and Adams, R., *J. Am. Soc.* **47**, 1047 (1925).
Clemo, G. R., and Melrose, T. A., *J. Chem. Soc.* p. 424 (1942).
Cohen, S., Thom, E., and Bendich, A., *J. Org. Chem.* **28**, 1379 (1963).
Cope, A. C., and Kagan, F., *J. Am. Chem. Soc.* **80**, 5499 (1958).
Corey, E. J., and Young, R. L., *J. Am. Chem. Soc.* **77**, 1672 (1955).
Csuros, Z., Zech, K., and Geczy, I., *Hung. Acta Chim.* **1**, 1 (1946).
Dauben, W. G., and Adams, R. E., *J. Am. Chem. Soc.* **70**, 1759 (1948).
DePuy, C. H., and Zaweski, E. F., *J. Am. Chem. Soc.* **81**, 4920 (1959).
Dunworth, W. P., and Nord, F. F., *J. Am. Chem. Soc.* **74**, 1459 (1952).
Eliel, E. L., and Lukach, C. A., *J. Am. Chem. Soc.* **79**, 5986 (1957).
Eliel, E. L., and Ro, R. S., *J. Am. Chem. Soc.* **79**, 5992 (1957).
Faillebin, M., *Compt. Rend.* **117**, 1118 (1923).
Findlay, S. P., *J. Org. Chem.* **24**, 1540 (1959).
Foresti, B., *Ann. Chim. Appl.* **27**, 359 (1937).
Foresti, B., *Soc. Ital. Progr. Sci. Atti 27th Riunione, Bologna* **5**, 346 (1939).
Freifelder, M., *J. Org. Chem.* **29**, 2895 (1964).
Freifelder, M., and Stone, G. R., *J. Org. Chem.* **26**, 3805 (1961).
Freifelder, M., Anderson, T., Ng, Y. H., and Papendick, V., *J. Pharm. Sci.* **53**, 967 (1964).
Hartung, W. H., and Chang, Y.-T., *J. Am. Chem. Soc.* **74**, 5927 (1952).
Hartung, W. H., and Crossley, F. S., *J. Am. Chem. Soc.* **56**, 158 (1934).
Hartung, W. H., and Simonoff, R., *Org. Reactions* **7**, 263 (1953).
Hasek, R. H., and Martin, J. C., *J. Org. Chem.* **28**, 1468 (1963).
Hasek, R. H., Elam, E. U., Martin, J. C., and Nations, R. G., *J. Org. Chem.* **26**, 700 (1961).
Hennion, G. F., and Watson, E. J., *J. Org. Chem.* **23**, 656 (1958).
Hiskey, R. G., and Northrop, R. C., *J. Am. Chem. Soc.* **83**, 4798 (1961).
Hornbaker, E. D., and Burger, A., *J. Am. Chem. Soc.* **77**, 5314 (1955).
House, H. O., Paragamian, V., and Wluka, D. J., *J. Am. Chem. Soc.* **82**, 2561 (1960).
Howard, W. L., and Brown, J. H., Jr., *J. Org. Chem.* **26**, 1026 (1961).
Hückel, W., and Hubele, A., *Ann. Chem.*, **613**, 27 (1958).
Huisgen, R., and Rauenbusch, E., *Ann. Chem.* **641**, 51 (1961).
Jeanloz, R., Prins, D. A., and Euw, J. V., *Helv. Chim. Acta* **30**, 374 (1947).
Jensen, F. R., *J. Org. Chem.* **25**, 269 (1960).
Johnson, W. S., Christiansen, R. G., and Ireland, R. E., *J. Am. Chem. Soc.* **79**, 1995 (1957).
Julian, P. L., Pikl, J., and Wantz, F. E., *J. Am. Chem. Soc.* **57**, 2026 (1935).
Karady, S., *J. Org. Chem.* **27**, 3720 (1962).
Kaye, I. A., and Matthews, R. S., *J. Org. Chem.* **28**, 325 (1963).
Kaye, I. A., and Matthews, R. S., *J. Org. Chem.* **29**, 1341 (1964).
Kindler, K., Schärfe, E., and Henrich, P., German Patent 817,459, Oct. 18, 1951.
Kindler, K., Oelschläger, H., and Henrich, P., *Chem. Ber.* **86**, 501 (1953).
Kindler, K., Günther, H., Helling, H., and Sussner, E., *Ann. Chem.* **605**, 200 (1957).
Koelsch, C. F., and Ostercamp, D. L., *J. Org. Chem.* **26**, 1104 (1961).
Kohler, E. P., and Davis, A. R., *J. Am. Chem. Soc.* **52**, 4520 (1930).
Koizumi, M., *Sci. Papers Inst. Phys. Chem. Res. (Tokyo)* **37**, 414 (1940).
Kollonitsch, J., Mertel, H. E., and Verdi, V. F., *J. Org. Chem.* **27**, 3362 (1962).
Koo, J., *J. Am. Chem. Soc.*, **75**, 720 (1953).

Kreutzberger, A., and Kalter, P. A., *J. Org. Chem.* **25**, 554 (1960).

Levine, M., and Temin, S. C., *J. Org. Chem.* **22**, 85 (1957).

Liberman, A. L., and Kazanskii, B. A., *Bull. Acad. Sci. URSS Classe Sci. Chim.* p. 77 (1946).

Linstead, R. P., and Levine, P., *J. Am. Chem. Soc.* **64**, 2022 (1942).

Linstead, R. P., and Thomas, S. L. S., *J. Chem. Soc.* p. 1127 (1940).

Lock, G., and Walter, E., *Chem. Ber.* **77**, 286 (1944).

Lyle, R. E., Leone, S. A., Troscianiec, H. J., and Warner, G. H., *J. Org. Chem.* **24**, 330 (1959).

Meschke, R. W., and Hartung, W. H., *J. Org. Chem.* **25**, 137 (1960).

Meyer, W. L., and Levinson, A. S., *J. Org. Chem.* **28**, 2184 (1963).

Mosettig, E., and Burger, A., *J. Am. Chem. Soc.* **57**, 2189 (1935).

Mosettig, E., and van de Kamp, J., *J. Am. Chem. Soc.* **55**, 3442 (1933).

Müller, H. K., Jarchow, I. I., and Rieck, G., *Ann. Chem.* **613**, 103 (1958).

Murphy, J. G., *J. Org. Chem.* **26**, 3104 (1961).

Nair, M. D., and Adams, R., *J. Org. Chem.* **26**, 3059 (1961).

Nielsen, A. T., Moore, D. W., Mazur, J. H., and Berry, K. H., *J. Org. Chem.* **29**, 2898 (1964).

Orchin, M., and Butz, L. W., *J. Am. Chem. Soc.* **65**, 2296 (1943).

Patrikeev, V. V., and Liberman, A. L., *Dokl. Akad. Nauk SSSR* **62**, 87 (1948).

Peppiatt, E. G., and Wicker, R. J., *J. Chem. Soc.* p. 3122 (1955).

Peterson, P. E., and Casey, C., *J. Org. Chem.* **29**, 2325 (1964).

Phillips, A. P., and Mentha, J., *J. Am. Chem. Soc.* **78**, 140 (1956).

Post, G. G., and Anderson, L., *J. Am. Chem. Soc.* **84**, 471 (1962).

Posternak, T., *Helv. Chim. Acta* **24**, 1045 (1941).

Rader, C. P., Wicks, G. E., Jr., Young, R. L., Jr., and Aaron, H. S., *J. Org. Chem.* **29**, 2252 (1964).

Rapala, R. T., and Farkas, E., *J. Am. Chem. Soc.* **80**, 1008 (1958).

Rebstock, M. C., Moersch, G. W., Moore, A. C., and Vandenbelt, J. M., *J. Am. Chem. Soc.* **73**, 3666 (1951).

Rosenmund, K. W., Karg, E., and Marcus, F. K., *Chem. Ber.* **75B**, 1850 (1942).

Roy, S. K., and Wheeler, D. M. S., *J. Chem. Soc.* p. 2155 (1963).

Rylander, P. N., and Steele, D. R., *Engelhard Ind. Tech. Bull.* **3**, 125 (1963).

Rylander, P. N., and Steele, D. R., *Engelhard Ind. Tech. Bull.* **5**, 113 (1965).

Rylander, P. N., and Steele, D. R., Unpublished observations, Engelhard Ind., Patent pending, 1966.

Rylander, P. N., Himelstein, N., and Kilroy, M., *Engelhard Ind. Tech. Bull.* **4**, 49 (1963).

Shriner, R. L., and Anderson, J., *J. Am. Chem. Soc.* **61**, 2705 (1939).

Shriner, R. L., and Witte, M., *J. Am. Chem. Soc.* **63**, 2134 (1941).

Shuikin, N. I., and Vasilevskaya, G. K., *Izv. Akad. Nauk SSSR Ser. Khim.* p. 557 (1964).

Smissman, E. E., Muren, J. F., and Dahle, N. A., *J. Org. Chem.* **29**, 3517 (1964).

Smith, H., *J. Chem. Soc.* p. 803 (1953).

Smith, L. I., and Holmes, R. R., *J. Am. Chem. Soc.* **73**, 3851 (1951).

Sonntag, N. O. V., Linder, S., Becker, E. I., and Spoerri, P. E., *J. Am. Chem. Soc.* **75**, 2283 (1953).

Stacey, G. W., and Mikulec, R. A., *J. Am. Chem. Soc.* **76**, 524 (1954).

Stevens, C. L., and Chang, C. H., *J. Org. Chem.* **27**, 4392 (1962).

Theilacker, W., and Drössler, H. G., *Chem. Ber.* **87**, 1676 (1954).

Vaughan, J. R., Jr., and Blodinger, J., *J. Am. Chem. Soc.* **77**, 5757 (1955).

Verzele, M., and Anteunis, M., *Bull. Soc. Chim. Belges* **68**, 315 (1959).

Verzele, M., Acke, M., and Anteunis, M., *J. Chem. Soc.* p. 5598 (1963).

Walker, G. N., *J. Am. Chem. Soc.* **78**, 3201 (1956).

Walker, G. N., *J. Org. Chem.* **23**, 133 (1958).

Weidlich, H. A., and Meyer-Delius, M., *Chem. Ber.* **74B**, 1195, 1213 (1941).

Werbel, L. M., Elslager, E. F., and Pearlman, W. M., *J. Org. Chem.* **29**, 967 (1964).

Weygand, C., and Werner, A., *Chem. Ber.* **71B**, 2469 (1938).
Wicker, R. J., *J. Chem. Soc.* p. 2165 (1956).
Wicker, R. J., *J. Chem. Soc.* p. 3299 (1957).
Wilt, J. W., and Schneider, C. A., *J. Org. Chem.* **26**, 4196 (1961).
Zirkle, C. L., Gerns, F. R., Pavloff, A. M., and Burger, A., *J. Org. Chem.* **26**, 395 (1961).

16

Reductive Alkylation—Preparation of Amines

Primary or secondary amines or ammonia may interact with aldehydes or ketones in the presence of hydrogen and a hydrogenation catalyst to produce a new amine. The amine and carbonyl compound form an addition product which may undergo hydrogenolysis directly or first undergo dehydration to an imine that is then reduced.

$$\text{RCHO} + \text{R}'\text{NH}_2 \rightleftharpoons \underset{\begin{subarray}{c} \updownarrow \\ \text{RCH}=\text{N}-\text{R}' \end{subarray}}{\overset{\text{RCH}-\text{NH}-\text{R}'}{\underset{\text{OH}}{|}}} \xrightarrow[\text{H}_2]{\text{H}_2} \text{RCH}_2\text{NHR}' + \text{H}_2\text{O}$$
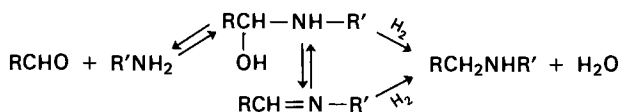
R′ = H, alkyl, aryl

Primary or secondary amines formed in a reductive alkylation are themselves suitable substrates for the reaction and may be further alkylated:

$$\text{RCH}_2\text{NHR}' + \text{RCHO} \longrightarrow (\text{RCH}_2)_2\text{NR}' + \text{H}_2\text{O}$$
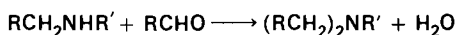
The reduction may yield a mixture of products, the composition of which is controlled to a considerable extent by the molar ratio of reactants. Alkylation tends to become more extensive as the molar ratio of carbonyl compound to amine is increased.

A requirement for a successful reductive alkylation is that hydrogenation of the carbonyl compound to an alcohol be a relatively slow step. To decrease the opportunity for alcohol formation, many workers allow the amine and carbonyl compound to stand together for some time to ensure their interaction before beginning the hydrogenation (Archer *et al.*, 1957), but this procedure is not always necessary or desirable (Heyl *et al.*, 1952). Various condensing or dehydrating agents may also be employed to ensure formation of the addition compounds. Another procedure is to isolate the intermediate imine before beginning the hydrogenation step (Emerson, 1948). (Reduction of imines is discussed in another chapter.)

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I. SUBSTRATES

The tendency for an amine and a carbonyl compound to interact initially and for the product to undergo hydrogenation is related inversely to steric hindrance in the neighborhood of the functions (Skita *et al.*, 1933). Reductive alkylation of ammonia with methyl ethyl ketone afforded twice as much secondary amine (37% yield) as with diethyl ketone (20% yield) (Skita and Keil, 1928). Cyclic ketones tend to produce more secondary amine on reductive alkylation than linear ketones of comparable carbon number; cyclopentanone and ammonia over platinum oxide afforded dicyclopentylamine in 71% yield (Hückel and Kupka, 1956). The yield of secondary amine formed by reductive alkylation over platinum of cyclohexylamine with acetone, methyl ethyl ketone, or diethyl ketone fell with increasing hindrance around the carbonyl function, being 79%, 60%, and 31%, respectively (Skita and Keil, 1928).

Table I compares the percentage of methylcyclohexylamines, bis(methyl-cyclohexyl)amines, and methylcyclohexanols formed in reductive alkylation

TABLE I

REDUCTIVE ALKYLATION OF AMMONIA WITH CYCLOHEXANONES[a]

Catalyst	Ketone	Moles ammonia per mole ketone	1° amine (% by weight)	2° amine (% by weight)	alcohol (% by weight)
5% Rh/C	4-Methylcyclohexanone	6	44	40	16
5% Ru/C	4-Methylcyclohexanone	6	0	0	100
5% Pd/C	4-Methylcyclohexanone	6	27	72	1
5% Pd/C	4-Methylcyclohexanone	1.25	8	91	1
5% Rh/C	2-Methylcyclohexanone	6	80	0	20
5% Ru/C	2-Methylcyclohexanone	6	39	4	57
5% Pd/C	2-Methylcyclohexanone	6	96	3	1
5% Pd/C	Cyclohexanone	6	4	96	0

[a] Temperature, 100°C; pressure, 1000 psig. Stirred autoclave. No solvent. Ammonia present as concentrated aqueous ammonia.

of ammonia with 2-methyl- and 4-methylcyclohexanones over 5% palladium-, 5% rhodium-, and 5% ruthenium-on-carbon (Steele and Rylander, 1962). Under the conditions of the reaction platinum-on-carbon was rapidly poisoned.
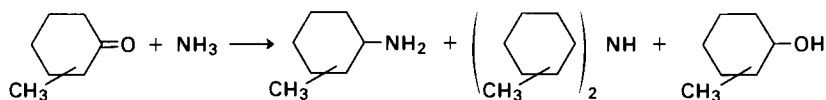
A methyl group in the 2-position offered a large amount of steric hindrance to formation of secondary amine, which did not exceed 4% of the total product. A single comparison of reductive alkylation of 4-methylcyclo-hexanone and cyclohexanone over 5% palladium-on-carbon suggests that secondary amine formation is impeded somewhat even by a methyl group in the 4-position. (These results are discussed further in Section II, A.)

Compounds with a tendency toward cyclization may undergo reductive alkylation with unusual ease. A tertiary amine was formed by interaction of a secondary aromatic amine and a carbonyl group of an imide in the conversion of rhetsinine to *dl*-evodiamine by hydrogenation over platinum oxide in acetic acid (Pachter and Suld, 1960).
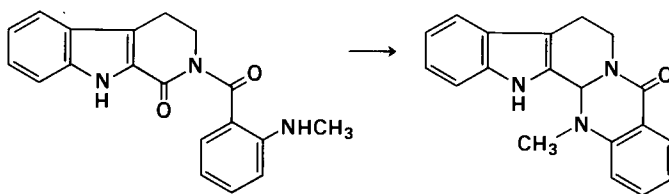
The yield of tertiary amines from reductive alkylation of aliphatic secondary amines is usually low (Emerson, 1948), due probably to steric hindrance. An exception to this generality has been reported by Wright (1959), who obtained excellent yields of tertiary amine from reductive alkylation of 2-unsubstituted merimine derivatives and cyclohexanone:
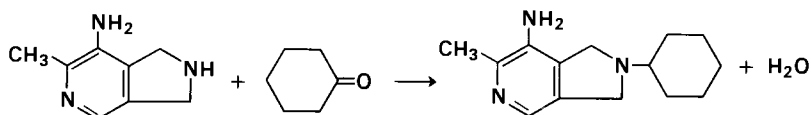
Alkylation, after absorption of one mole of hydrogen, had occurred almost exclusively in the 2-position even when a large excess of carbonyl compound was present. The 7-amino group could be alkylated also if the reduction were much prolonged. In these reductions a mixture of 5% palladium-on-carbon and 10% platinum-on-carbon gave a faster rate and better yields than 5% palladium-on-carbon alone.

A. TERTIARY AROMATIC AMINES

Reductive methylation has been seldom used as a means of preparation of tertiary aromatic amines because of facile nuclear condensation, but the reaction may be quite successful if suitable techniques are employed (Pearson and Bruton, 1951). For example, *p*-aminoacetophenone (0.1 mole) in 80 ml 95% ethanol and 5 ml concentrated hydrochloric acid was cooled to 5°C.

In another flask 0.2 mole of 40 % formalin was also cooled; then the contents of both flasks were mixed in a hydrogenation bottle containing 150 mg pre-reduced platinum oxide, and the reduction carried out at 45 psig to afford *p*-dimethylaminoacetophenone in 70 % yield. The yields were lower if there were a delay in hydrogenation after mixing all the components, if the molar ratio of formalin were increased, if the acid concentration were decreased, and if the catalyst were reused. An alternative procedure was to use a limited amount of trioxane, which generates formaldehyde slowly during the reduction. Early attempts to prepare this compound had resulted in a maximum yield of 3 %.

$$H_2N - \underset{\text{}}{\bigcirc} - \underset{\underset{O}{\|}}{C} - CH_3 \;+\; CH_2O \;\longrightarrow\; (CH_3)_2N - \underset{\text{}}{\bigcirc} - \underset{\underset{O}{\|}}{C} - CH_3 \;+\; H_2O$$
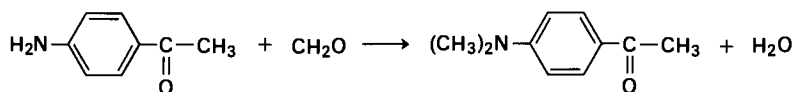
B. Condensing Agents

With certain combinations of amine and carbonyl compound, interaction to form an addition compound or imine does not occur readily and reductive alkylation of such systems fails. For example, aldehydes and anhydrous 5-aminotetrazole do not react to a significant extent under the usual conditions employed for synthesis of azomethines. In the presence of an added base, as triethylamine or guanidine, condensation occurs readily and the product is easily reduced over platinum oxide in anhydrous alcohol (Henry and Finnegan, 1954).

$$\begin{matrix} N\!-\!NH \\ \| \quad\; \diagdown \\ \quad\;\;\; C\!-\!NH_2 \\ N\!-\!N \diagup \end{matrix} + RCHO \;\xrightarrow{H_2}\; \begin{matrix} N\!-\!NH \\ \| \quad\; \diagdown \\ \quad\;\;\; C\!-\!NHCH_2R \\ N\!-\!N \diagup \end{matrix} + H_2O$$
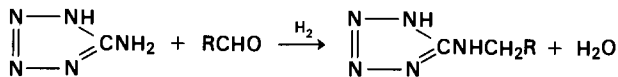
Acidic condensing agents are also used. Dialkyl 4-amino-1-phenyl-2,3-dimethyl-5-pyrazolones have been formed by reductive alkylation in the presence of platinum-on-barium sulfate and acids such as zinc chloride, hydrochloric acid, or acetic acid. A mixture of 10 gm 4-isopropylamino-1-phenyl-2,3-dimethyl-5-pyrazolone in ethanol, 30 ml acetone, and 1 gm zinc chloride, maintained at 0°C for 2 hours, was hydrogenated in the presence of 10 gm 10 % platinum-on-barium sulfate at room temperature and 3.5 atm to give the 4-diisopropylamine compound (Skita and Stühmer, 1955).

Formation of intermediate imines may be facilitated by use of drying agents, such as calcium oxide or anhydrous magnesium sulfate. Reductive alkylation of pyrrolidine with deoxybenzoins was achieved by use of calcium oxide. A mixture of 0.2 mole of deoxybenzoin, 0.24 mole of pyrrolidine, and 30 gm calcium oxide was heated on a steam bath for 20 hours. To this was added 100 ml anhydrous ethanol, the mixture filtered, and the filtrate reduced

over 0.2 gm platinum oxide. Without calcium oxide treatment, reductive alkylation did not occur (Heinzelman and Aspergren, 1953). A series of N-cycloalkylcyclopropyl amines was prepared by reductive alkylation of cyclopropylamine with a cycloalkanone over platinum oxide in thiophene-free benzene. Before hydrogenation was begun the amine and ketone in benzene were allowed to stand an hour, then anhydrous magnesium sulfate was added, and the mixture allowed to stand another hour to complete formation of the intermediate imine (Freifelder and Horrom, 1963).

$$(CH_2)_n \hspace{-0.5em} \diagdown \hspace{-0.5em} C{=}O \; + \; NH_2 {-} \triangleleft \; \longrightarrow \; (CH_2)_n \hspace{-0.5em} \diagdown \hspace{-0.5em} CH{-}NH{-}\triangleleft \; + \; H_2O$$

$$n = 1 - 4$$
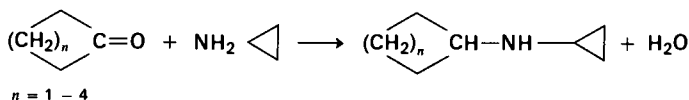
II. CATALYSTS

Platinum catalysts are used much more frequently than any other platinum metal in reductive alkylation of amines. An excellent comprehensive survey of reductive alkylation, made in 1948 (Emerson), revealed that platinum catalysts were used more than ten times as often as palladium. Platinum catalysts are still used most frequently, but evidently this preference for platinum stems from established precedent rather than a demonstrated superiority; reports comparing the effectiveness of various platinum metals are rare indeed. Cope and Hancock (1942) reported that platinum oxide is definitely superior to 10% palladium-on-carbon (Hartung, 1928) but, since the procedure used for preparation of the palladium catalyst gives a catalyst of low activity, it is perhaps not safe to generalize from these results.

Platinum oxide itself is perhaps not a catalyst for reductive alkylation. Unless the catalyst is reduced prior to contacting the substrates, lengthy induction periods may ensue (Cope and Hancock, 1942). Failure to pre-reduce the catalyst has in some cases led to diminished yields as well as longer reduction times (Manske and Johnson, 1929). Reduction of platinum oxide in concentrated aqueous ammonia at ambient conditions is said to proceed very slowly if at all (Iles and Worrall, 1961). On the other hand, prereduction of platinum oxide is not always necessary; rapid reductive alkylations have been achieved when platinum oxide was used without this additional step (Freifelder, 1963).

A. EFFECT OF CATALYST ON SELECTIVITY

The products obtained in a reductive alkylation may depend importantly on the catalyst used, as illustrated by the data of Table I, which compares

5% palladium-, 5% rhodium-, and 5% ruthenium-on-carbon in reductive amination of methylcyclohexanones. In the case of 4-methylcyclohexanone, where steric hindrance is not a major factor, ruthenium produces exclusively alcohol, palladium the most secondary amine, and rhodium the most primary amine. Secondary amine formation in reductive amination of 2-methylcyclohexanone is strongly impeded by steric hindrance, and the product composition is determined consequently by the relative rates of formation of primary amine and alcohol. Viewed in this way, the results for the two series are not so anomalous as they first appear.

One interpretation for the widely different percentages of primary and secondary amines found in reductive amination of 4-methylcyclohexanone is that condensation reactions as well as hydrogenations occur on the catalyst surface. Other workers, on different grounds, have made a similar suggestion. Klebanskii and Vilesova (1958) observed that the reductive alkylation of hexamethylenediamine with butyraldehyde, in ethanol over platinum, proceeds more rapidly than hydrogenation of the corresponding Schiff base, suggesting that the latter cannot be an intermediate in the reductive alkylation. They suggested that the substrates are individually adsorbed on the catalyst surface prior to interaction, and that the rate of reduction is determined by the rate of chemisorption of the individual reactants.

B. CHOICE OF CATALYST

The catalyst of choice may be determined in part by the presence of other functional groups present in the substrate. Reductive alkylation of aromatic or aliphatic diketones over platinum tends to afford an amino alcohol; over palladium, one carbonyl remains unreduced and an amino ketone is formed. The results depend partly on the amount of catalyst used; larger amounts of catalyst cause more extensive hydrogenation (Skita et al., 1933). If either reactant in a reductive alkylation contains an aryl halogen, platinum would be preferred to palladium provided the halogen is to be retained. For instance, a mixture of 1-(4-chlorophenyl)-2-propanone (I) and benzylamine in absolute ethanol reduced over 5% platinum-on-carbon gave the alkylated product (II) in 78% yield with little loss of halogen. Even over platinum, dehydrohalogenation was extensive if the reduction were not stopped (Freifelder et al., 1964).

(I)   (II)
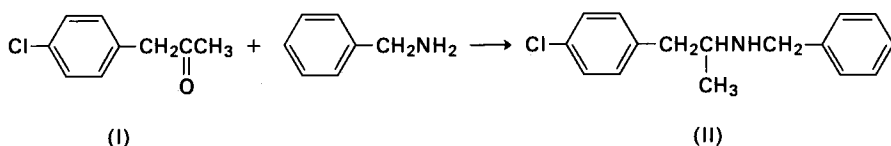
Platinum oxide in acetic acid proved to be the system of choice for reductive cyclization of III to V. Saturation of the pyridine ring must precede reduction to the hydroxylic compound (IV), for it was shown that IV did not undergo cyclization to V. Reduction over platinum oxide in ethanol afforded a mixture of IV and V; over palladium-on-carbon in ethanol only the double bond of III was reduced (Sam et al., 1964).
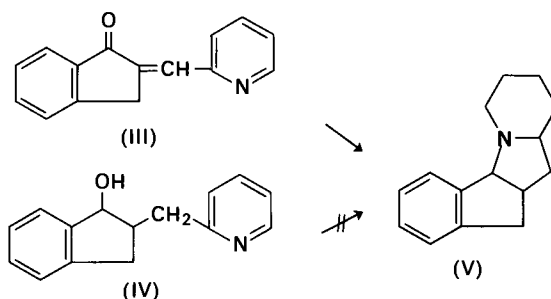
Ruthenium catalysts might be preferred if the simultaneous reduction of another function, particularly an aromatic one, is required as well. For instance, hydrogenation of furfurylidene-acetone over ruthenium dioxide at 170°C and 1700 psig in alcoholic ammonia solution gave the corresponding saturated amine in 61 % yield (Ponomarev and Chegolya, 1962).

C. SULFIDED PLATINUM METAL CATALYSTS

An unusual type of catalyst (Belgian Patent 643,911) has given excellent results in reductive alkylation of anilines (Dovell and Greenfield, 1965). These catalysts are platinum metal sulfides usually on a support. In general, they behave like the base metal sulfide catalysts but are much more active and more stable under hydrogenation conditions. In a typical reductive alkylation, a 600-ml stainless steel autoclave is charged with 158 gm (0.86 mole) N-phenyl-p-phenylene-diamine, 95.2 gm (0.95 mole) methyl isobutyl ketone, and 3.2 gm 5% platinum sulfide-on-carbon.* The autoclave is purged and maintained under hydrogen at 175–180°C and 405–615 psig for 4.5 hours. The catalyst is removed by filtration and, after topping under 32-mm pressure at 188°C, 228 gm (99% yield) N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine is obtained as a residue (Dovell and Greenfield, 1965).
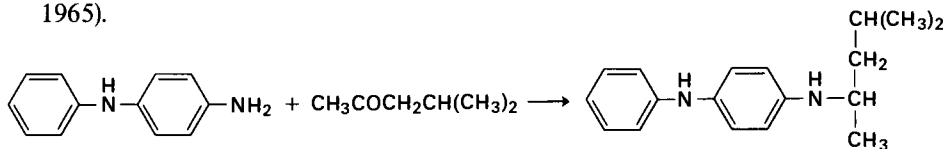
* Manufactured by Engelhard Industries, Newark, N.J.

These catalysts are particularly resistant to poisoning and can be used with substrates of low quality that would poison most other catalysts. This is an especially important point for industrial operation where substrate purification is to be avoided if possible. Despite the severity of the reduction conditions, ring saturation does not occur over these catalysts.

III. STEREOCHEMISTRY

Reductive alkylation with optically active substrates may afford compounds containing new optically active centers. The magnitude of the induced asymmetry may depend both on the structure of the substrate and on the catalyst used (Hiskey and Northrup, 1961). One can usually predict the enantiomer that will predominate, if the assumptions are made that hydrogen is adsorbed on and added from the catalyst, that the catalyst approaches the substrate from its least hindered side (Prelog, 1956), and that the intermediate species undergoing reduction is the imine and not the hydroxyamino addition compound. (Certain aspects of stereospecific reductions of optically active imines have been discussed in the chapter on imine hydrogenation.)

Hiskey and Northrup (1961) reductively alkylated four α-keto acids in the presence of $D(+)$- and $L(-)$-α-methylbenzylamine and, after hydrogenolysis of the benzyl moiety, obtained the corresponding optically active α-amino acids in reasonable yield.

$$
\overset{*}{R}CCOOH + C_6H_5\overset{*}{C}HCH_3 \xrightarrow{H_2}
\begin{array}{c}
\overset{*}{R}CHCOOH \\
| \\
NH \\
\overset{*}{|} \\
CH_3\!-\!CH \\
| \\
C_6H_5
\end{array}
\xrightarrow{H_2} \overset{*}{R}CHCOOH
$$
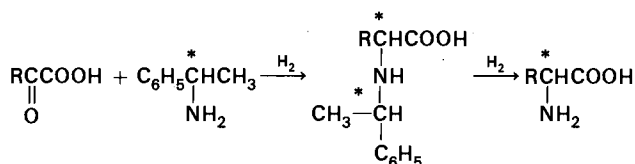
Reductive alkylation of the free acids proceeded better than alkylation of esters; interaction of benzyl pyruvate with $L(-)$-α-methylbenzylamine produced bimolecular condensation and only low yields of $L(+)$-alanine. This side-reaction was minimized when the free acids were employed. In the examples studied, the configuration of the α-amino acid produced was the same as that of the α-methylbenzylamine from which it was derived. The magnitude of the induced asymmetry apparently depends on the nature of the alkyl portion of the keto acid; as the size of the alkyl group increased, the optical purity of the enantiomer produced decreased. The optical purity depends also on the catalyst; reductive alkylation of 2-oxobutyric acid and optically active α-methylbenzylamine over palladium-on-carbon, over palladium hydroxide-on-carbon, and over platinum oxide

produced in the resulting amino acid an 81.4, 71.7, and 56.3 total percent of excess enantiomorph, respectively.

Part of the enhanced ability of the palladium catalysts to promote asymmetric induction may stem from contributions by the support, which forces a more highly oriented approach of the substrate to active catalytic centers. The active sites on the catalyst surface may themselves be asymmetric, randomly present in equal numbers of mirror images (Beamer et al., 1960). In support of this contention, it was shown that, for equal rates of hydrogenation, twice as much catalyst was required to reduce the imine derived from benzylamine and a D(−)-acyloin as that derived from the racemic acyloin. Presumably catalyst sites of only one of the mirror images were available for reduction of the optically active compound.

Reductive alkylations have been carried out in which both the amine and carbonyl moieties were optically active (Hiskey and Northrop, 1965). Alanyl-L-alanine was prepared by hydrogenation of N-pyruvyl-L-alanine in the presence of D-α-methylbenzylamine over palladium-on-carbon, followed by catalytic debenzylation:
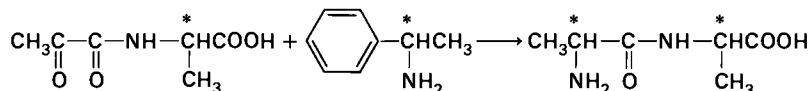
The results of this and other experiments indicated that the asymmetric center present in the N-pyruvyl-L-alanine had virtually no part in determining the stereochemistry at the new asymmetric center. Reductive amination of N-pyruvyl-L-alanine in the absence of another asymmetric center (i.e., with benzylamine) produced, contrary to expectation, more D-alanyl-L-alanine than the LL-isomer. The authors suggested that the stereochemical course of the reduction may be directed by a cyclized form.

IV. INCIPIENT AMINE AND CARBONYL COMPOUNDS

Reduction alkylations may be carried out with substrates that are not carbonyl compounds or amines but can be transformed to compounds of this type during the course of reduction. Functions reducible to amines include azo, hydrazo, nitro, nitroso, oxime, and hydroxylamines. Phenols, acetals, or ketals may provide precursors for carbonyl compounds.

A. Amine Precursors

Aromatic nitro compounds may be used in reductive alkylations. Emerson and Uraneck (1941) obtained N,N-di-n-butylaniline in 69% yield by hydrogenation of 0.1 mole of nitrobenzene and 0.3 mole of butyraldehyde in 10 ml

acetic acid and 150 ml 95% ethanol over 0.1 gm platinum oxide. Nitrobenzene is readily reduced to aniline over platinum oxide, but aniline is not necessarily an intermediate in the reduction. It was suggested that the compound that undergoes reductive alkylation is phenylhydroxylamine rather than aniline:
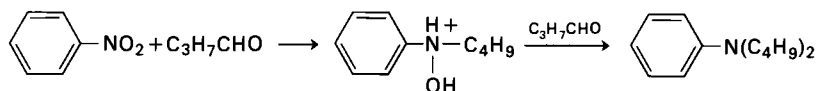
In support of this suggestion, it was shown that alkylaryl hydroxylammonium ions are far more reactive in reductive alkylation than the corresponding alkylaryl ammonium ions. N-Benzylphenylhydroxylamine, reduced in the presence of two equivalents of n-butyraldehyde in acid solution, afforded N-benzyl-N-n-butylaniline in 38% yield, whereas under the same conditions N-benzylaniline afforded only 3% of this tertiary amine. In further support of the contention that aniline is not an intermediate in the reductive alkylation is the observation that tertiary amines may be formed in the presence of very mild acidic condensing agents, such as trimethylamine hydrochloride, when nitrobenzene is the substrate, but that formation of tertiary amines requires concentrated hydrochloric acid or boiling formic acid when the substrate is aniline (Emerson and Uraneck, 1941).

Secondary amines are formed by the hydrogenation of aromatic nitro compounds in the presence of ketones. N-Isopropylaniline was obtained in 53% yield by hydrogenation of nitrobenzene in acetone over platinum oxide in acetic acid. The behavior of aliphatic nitro compounds parallels that of the aromatic. Tertiary amines were formed in 45–92% yield by hydrogenation of nitromethane in the presence of acetaldehyde, propionaldehyde, or n-butyraldehyde, whereas the secondary amine, isopropylmethylamine, was obtained in 59% yield when nitromethane was alkylated with acetone. Reduction of aromatic nitroacids in the presence of aqueous formaldehyde affords N-methylated amino acids (Bowman and Stroud, 1950). Other aldehydes may be used as well, giving mono- or di-alkylated products depending on steric considerations (Bowman, 1950a). Polypeptides undergo alkylation only at the terminal amino group (Bowman, 1950b). Reductive methylation of syn- and anti-2-nitro-9,10-dihydroanthracene-9,10-endo-α,β-succinic anhydrides over platinum oxide afforded the corresponding dimethylamino compounds in 79% and 82% yields, respectively (Kaplan and Conroy, 1963).

Reductive alkylations may be carried out in a disproportionation reaction, using a nitro compound as a source of amine and a six-membered alicyclic ketone as a source of hydrogen. For instance, 0.1 mole of nitrobenzene was heated with 0.65 mole of cyclohexanone and 2 gm 5% palladium-on-carbon at 161–172°C for 5 hours, water being removed from the reaction mixture

as formed. The yield of diphenylamine was 95% of theoretical with traces of aniline and N-cyclohexylaniline. Phenol is a major byproduct. The reaction was also carried out with p-nitrophenetole or N-isopropyl-p-nitroaniline and cyclohexanone. The inventors consider that two moles of nitro compound and three moles of ketone produce two moles of product, one mole of phenol, and six moles of water. It is therefore desirable to use at least 1.5 moles of ketone per mole of nitro compound (Kilbrourne et al., 1965).
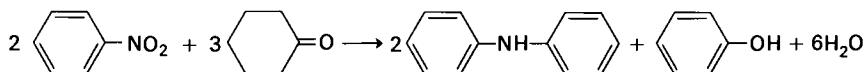
Azo compounds may also be used in reductive alkylations. For instance, a number of benzenediazonium salts were coupled with aromatic amines, and the resulting aminoazo compounds were catalytically reduced in the presence of a ketone over 30% platinum-on-carbon at elevated temperatures and pressures (British Patent 771,063):
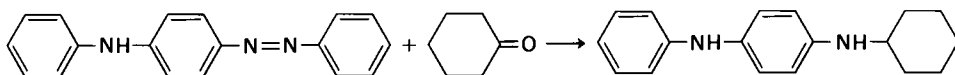
Aromatic azo compounds are easily reduced to aromatic amines but the amine is not necessarily an intermediate in the reduction. It has been suggested (Emerson et al., 1941) that the azo function is reduced to a hydrazo compound, which then condenses with the carbonyl compound. Hydrogenolysis of this condensed product affords the alkylated aniline.

B. CARBONYL PRECURSORS

Acetals and ketals have been used instead of aldehydes and ketones in reductive alkylations. A mixture of 0.51 mole of acetamide, 0.525 mole of 1,1-diethoxyethane, 200 ml acetic acid, and 6 gm concentrated sulfuric acid was shaken with 2 gm 10% palladium-on-carbon at 40 psig initial pressure. After neutralization and fractionation, N-ethylacetamide was obtained in 45% yield. The use of acetamide, acetal, or 2,2-dimethoxypropane gave N-ethyl- and N-isopropylacetamide in about 50% yield (Johnson and Crosby, 1962).

$$CH_3CONH_2 + CH_3CH(OC_2H_5)_2 \longrightarrow CH_3CONHC_2H_5$$
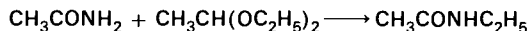
The acetal group may also protect an aldehyde group during reductive alkylation. Its subsequent hydrolysis frees it for further use. A convenient synthesis of 1,2,3,4-tetrahydroisoquinolines involves reductive alkylation

over platinum oxide of amino-acetal with an appropriate aldehyde to yield an *N*-benzylamino-acetal. This secondary amine is then treated with dilute hydrochloric acid and catalytically reduced over palladium-on-carbon. The yields of tetrahydroisoquinoline from vanillin, isovanillin, and ortho-vanillin were 71%, 67%, and 75%, respectively, based on starting aldehydes (Bobbitt *et al.*, 1964).
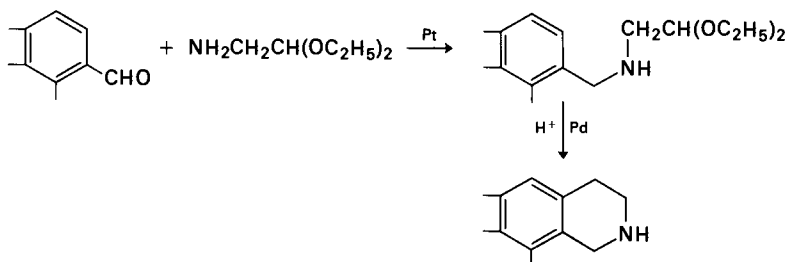
Partial hydrogenation of phenols affords cyclohexanones, sometimes in excellent yields, if the reduction is properly moderated. Phenols might therefore be expected to be suitable carbonyl precursors in reductive alkylations, and have in fact been so used with success. Dicyclohexylamine has been produced in yields of 75% by hydrogenation of a mixture of aniline and phenol at 100–200°C and 120–200 psig or greater over a palladium-on-carbon catalyst (Dankert and Permoda, 1951). Other workers have specifically claimed pressures of 100 psig or less in this reduction (Belgian Patent, 627,187).

REFERENCES

Archer, S., Lewis, T. R., Unser, M. J., Hoppe, J. O., and Lape, H., *J. Am. Chem. Soc.* 79, 5783 (1957).

Beamer, R. L., Smith, J. D., Andrako, J., and Hartung, W. H., *J. Org. Chem.* 25, 798 (1960).

Bobbitt, J. M., Khanna, K. L., and Kiely, J. M., *Chem. Ind. (London)* p. 1950 (1964).

Bowman, R. E., *J. Chem. Soc,* p. 1346 (1950a).

Bowman, R. E., *J. Chem. Soc.* p. 1349 (1950b).

Bowman, R. E., and Stroud, H. H., *J. Chem. Soc.* p. 1342 (1950).

Cope, A. C., and Hancock, E. M., *J. Am. Chem. Soc.* 64, 1503 (1942).

Dankert, L. J., and Permoda, D. A., U.S. Patent 2,571,016, Oct. 9, 1951.

Dovell, F. S., and Greenfield, H., *J. Am. Chem. Soc.* 87, 2767 (1965).

Emerson, W. S., *Org. Reactions* 4, 174 (1948).

Emerson, W. S., and Uraneck, C. A., *J. Am. Chem. Soc.* 63, 749 (1941).

Emerson, W. S., Reed, S. K., and Merner, R. R., *J. Am. Chem. Soc.* 63, 972 (1941).

Freifelder, M., *J. Med. Chem.* 6, 813 (1963).

Freifelder, M., and Horrom, B. W., *J. Pharm. Sci.* 52, 1191 (1963).

Freifelder, M., Ng, Y. H., and Helgren, P. F., *J. Med. Chem.* 7, 381 (1964).

Hartung, W. H., *J. Am. Chem. Soc.* 50, 3372 (1928).

Heinzelman, R. V., and Aspergren, B. D., *J. Am. Chem. Soc.* 75, 3409 (1953).

Henry, R. A., and Finnegan, W. G., *J. Am. Chem. Soc.* 76, 926 (1954).

Heyl, D., Luz, E., Harris, S. A., and Folkers, K., *J. Am. Chem. Soc.* **74**, 414 (1952).

Hiskey, R. G., and Northrop, R. C., *J. Am. Chem. Soc.* **83**, 4798 (1961).

Hiskey, R. G., and Northrop, R. C., *J. Am. Chem. Soc.* **87**, 1753 (1965).

Hückel, W., and Kupka, R., *Chem. Ber.* **89**, 1694 (1956).

Iles, R. W., and Worrall, W. S., *J. Org. Chem.* **26**, 5233 (1961).

Johnson, H. E., and Crosby, D. G., *J. Org. Chem.* **27**, 2205 (1962).

Kaplan, F., and Conroy, H., *J. Org. Chem.* **28**, 1593 (1963).

Kilbrourne, H. W., VanVerth, J. E., and Wilder, G. R., U.S. Patent 3,219,703, Nov. 23, 1965.

Klebanskii, A. L., and Vilesova, M. S., *Zh. Obshch. Khim.* **28**, 1767 (1958).

Manske, R. H. F., and Johnson, T. B., *J. Am. Chem. Soc.* **51**, 580 (1929).

Pachter, I. J., and Suld, G., *J. Org. Chem.* **25**, 1680 (1960).

Pearson, D. E., and Bruton, J. D., *J. Am. Chem. Soc.* **73**, 864 (1951).

Ponomarev, A. A., and Chegolya, A. S., *Dokl. Akad. Nauk SSSR* **145**, 812 (1962).

Prelog, V., *Bull. Soc. Chim. France* p. 987 (1956).

Sam, J., England, J. D., and Alwani, D. W., *J. Med. Chem.* **7**, 732 (1964).

Skita, A., and Keil, F., *Chem. Ber.* **61B**, 1452 (1928).

Skita, A., and Stühmer, W., German Patent 932,677, Sept. 5, 1955.

Skita, A., Keil, F., and Baesler, E., *Chem. Ber.* **66B**, 858 (1933).

Steele, D. R., and Rylander, P. N., Unpublished observations, Engelhard Ind. 1962.

Wright, W. B., Jr., *J. Org. Chem.* **24**, 1016 (1959).

17

Reductive Alkylation—Alkylidene Derivatives

Active methylene compounds may condense with aldehydes or ketones in the presence of hydrogen and a catalyst to afford the corresponding alkyl derivatives. Alternatively, the condensation may be carried out first, followed by reduction of the resulting carbon–carbon double bond. Palladium is the most popular catalyst for this reaction; platinum has been used occasionally, and apparently other platinum metal catalysts have not been used at all. This subject has been reviewed, and the compounds produced through 1952 from malonic esters, cyanoacetic esters, and acetonitriles have been tabulated (Cope et al., 1957).

Typical procedures for reductive alkylation of ethyl cyanoacetate have been given by Alexander and Cope (1944). The optimum experimental conditions vary somewhat according to the type of carbonyl compound used. Piperidine acetate and acetic acid were used as condensing agents with aldehydes, and ammonium acetate in acetic acid with ketones. Reductive alkylation of ethyl cyanoacetate with lower molecular weight aldehydes generally gave yields of 90% or better. Typically, a mixture of 0.5 mole of ethyl cyanoacete, 0.6 mole of freshly distilled aldehyde, 100 ml acetic acid, and 0.02 mole of piperidine was reduced immediately after mixing over 1 gm palladium-on-carbon. If the mixture is allowed to stand before reduction is begun, the yield may be lower. The yield of ethyl n-propylcyanoacetate dropped from 94% to 61% when the solution was allowed to stand 1 hour before hydrogenation was begun. A modification of the reductive alkylation procedure consists in using a 2-fold molar excess of ethyl cyanoacetate (Bachmann and Fornefeld, 1950).

$$RCHO + CH_2(CN)COOC_2H_5 \xrightarrow{H_2} RCH_2CH(CN)COOC_2H_5 + H_2O$$
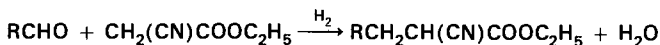
The most suitable solvent for the reductive alkylation varied with the carbonyl compound (Alexander and Cope, 1944). Alcohol proved to be the most satisfactory for ketones, dioxane for higher aldehydes, and acetic acid

for lower molecular weight aldehydes, such as acetaldehyde, propionalde-
hyde, and butyraldehyde. Palladium catalysts were superior to platinum
oxide or Raney nickel; over platinum oxide partial reduction of the nitrile
group occurred, and Raney nickel was deactivated by acetic acid in the
reaction mixture. Overhydrogenation is a possible side-reaction even when
palladium catalysts are used; in reduction of ethyl (1-indanylidene)cyano-
acetate over palladium-on-carbon, 133% of the theoretical hydrogen was
absorbed (Cope and Field, 1949).

REFERENCES

Alexander, E. R., and Cope, A. C., *J. Am. Chem. Soc.* **66**, 886 (1944).
Bachmann, W. E., and Fornefeld, E. J., *J. Am. Chem. Soc.* **72**, 5529 (1950).
Cope, A. C., and Field, L., *J. Am. Chem. Soc.* **71**, 1589 (1949).
Cope, A. C., Holmes, H. L., and House, H. O., *Org. Reactions* **9**, 145 (1957).

18

Carbocyclic Aromatics

This chapter is limited to hydrogenation of aromatics not bearing amino, hydroxy, alkoxy, or halogen substituents (the hydrogenation of anilines, phenols, and aromatic halogen compounds is discussed in other appropriate chapters).

I. COMPARISON OF CATALYSTS

The carbocyclic aromatic nucleus may be hydrogenated readily over platinum metal catalysts. Platinum, usually as platinum oxide, and rhodium are used frequently under mild conditions, whereas ruthenium and palladium catalysts are used mostly at elevated temperatures and pressures. A comparison of 5% iridium-, palladium-, platinum-, rhodium-, and ruthenium-on-carbon for hydrogenation of benzene is given in Table I. Rhodium and ruthenium are outstandingly good with this particular substrate, but the differences in

TABLE I

HYDROGENATION OF BENZENE [a]

| Catalyst | Rate of hydrogenation (ml H_2 absorbed per minute) | | | | |
	No solvent	Water	Acetic acid	Dimethyl-formamide	Methanol
Ir	< 10	—	—	< 10	< 10
Pd	< 10	< 10	< 10	< 10	< 10
Pt	< 10	< 10	< 10	< 10	< 10
Rh	765	906	118	70	625
Ru	1000	1050	33	< 10	221

[a] 300 mg 5% metal-on-carbon, 25°C, 1000 psig; 50 ml benzene without solvent, or 25 ml each of benzene and solvent.

rate among these catalysts are not always so large, as can be seen from the data of Tables III, IV, and V related to the hydrogenation of benzoic acid, biphenyl, and diphenylmethane. Ring substituents may also have a marked effect on the relative activity of platinum metal catalysts. For instance, this 5% iridium-on-carbon had a low activity for hydrogenation of benzene and aniline, but high activity for reduction of phenol.

A. PROMOTERS AND INHIBITORS

Hydrogenation of aromatic rings over platinum metal catalysts is influenced, sometimes to an extraordinary extent, by trace materials, a fact early recognized (Adams and Marshall, 1928). Phenanthrene purified by distillation over sodium, treatment with maleic anhydride, recrystallization, and sublimation resisted hydrogenation over platinum oxide, whereas phenanthrene purified by bromination and conversion to 9-phenanthroic acid was readily reduced (Burger and Mosettig, 1936). Reports such as this emphasize the possible gross errors inherent in the numerous correlations between substrate structure and rate of catalytic hydrogenation.

Traces poisons may also change the depth of reduction. Hydrogenation of quinoxaline over 5% rhodium-on-alumina in absolute ethanol at 100°C and 2000 psig afforded *cis*-decahydroquinoxaline in 93% yield, if the apparatus were scrupulously clean; otherwise only the hetero ring was reduced (Broadbent *et al.*, 1960).
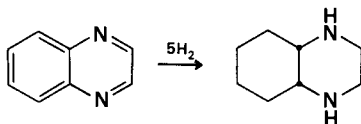
Ferrous chloride in dilute hydrochloric acid was a strong promoter in reduction of 1,2-benzanthracene over platinum oxide in ethanol. No reduction occurred over a catalyst prepared from pure ammonium chloroplatinate until the iron salt was added, and then reduction proceeded rapidly (Fieser and Hershberg, 1937, 1938). In larger amounts, iron is an inhibitor rather than a promoter for aromatic ring reduction; the use of iron additives in reduction over platinum oxide has been recommended when ring saturation is to be avoided (Weygand and Werner, 1938). Reduction of benzene over platinum oxide is said, without elaboration, to be promoted by certain organic quaternary ammonium salts (Keenan *et al.*, 1954).

Acids may be either promoters or inhibitors, depending on the catalyst and substrate. Hydrochloric acid was a strong inhibitor for reduction in methanol of toluene or benzoic acid over 5% rhodium-on-carbon or alumina (Freifelder, 1961); over platinum oxide, hydrochloric acid, even in trace

amounts, may be a powerful promoter (discussed in next section). Hydrogen iodide and hydrogen bromide were poisons for reduction of arylphosphonic and diaryl phosphinic acids over rhodium-on-alumina (Freedman *et al.,* 1955; Freedman and Doak, 1959). Small amounts of acetic acid strongly promoted reduction of certain aromatics over rhodium-on-alumina in methanol (Stocker, 1962).

An especially thorough study of the effect of poisons on the high pressure perhydrogenation of rosin was made by Montgomery *et al.* (1958). Rosin contains about 13% of dehydroabietic acid and similar compounds with highly hindered, difficult-to-reduce aromatic rings.
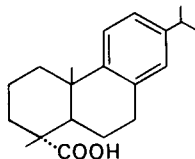
Any attempt at hydrogenation causes formation of more of this material through disproportionation of abietic-type acids. Of the conventional hydrogenation catalysts, only palladium, rhodium, and ruthenium had sufficient activity, palladium being apparently the most active of all. Both carbon monoxide and carbon dioxide were shown to be temporary poisons in this reduction, and the authors suggested that palladium and rhodium appeared to be better than ruthenium, not because of a greater intrinsic activity but because palladium and rhodium caused less decarboxylation of the rosin, and thus poisoned themselves less. The poisoning effects of these gases could be offset by periodically flushing the reactor, a technique of wide applicability.

The effect of extraneous metal ions and of sulfur on the activity of 5% palladium-on-carbon in rosin hydrogenation was evaluated, with surprising results. The metal ions were introduced into the system as nitrate salts and the sulfur as hydrogen sulfide with a weight ratio of poison to palladium of 60:1,000,000. Evaluations were carried out at an operating pressure of 5000 psig and 225°C. Rates of reduction with the extraneous metals were plotted as a percentage of the rate for the unmodified reduction, with the following results (figures, taken from a bar graph, are approximate): Al (23%), S (30%), Mg (50%), Na (50%), Zn (60%), Cu (63%), Ti (63%), Mn (70%), Si (72%), Pb (76%), Cr (76%), Hg (78%), Ni (78%), Sn (82%), and Ca (100%). Aluminum, magnesium, and sodium, usually not considered particularly toxic, were very objectionable, while lead and mercury, usually severe poisons, were much less so. The apparent poisoning effect of alumina, magnesium, and sodium is magnified by their low molecular weights; the order of relative toxicity on a molar concentration basis was Pb, Hg, Zn, Cu, S, Al, Mn, Ti, Sn, Mg, Na, Cr, Ni, Si, and Ca.

B. SODIUM CONTENT OF PLATINUM OXIDE

The rate of hydrogenation of benzene over platinum oxide has been shown to be very sensitive to traces of sodium in the catalyst. Platinum oxide as ordinarily prepared contains small amounts of sodium salts and such catalysts have been shown to be ineffective for reduction of benzene in neutral solvent or without solvent. These catalysts could be made active by pre-reduction in acetic acid or methanol followed by thorough rinsing (Keenan et al., 1954). The effectiveness of acidic solvents, such as acetic acid (Adams and Marshall, 1928), was attributed to their interaction with the sodium component in the catalyst. The effect of acidic solvents may be pronounced; benzene could not be reduced even at 2000 psig and 180°C in ethanol or dioxane over platinum oxide, but in acetic acid the reduction proceeded readily under mild conditions (Baker and Schuetz, 1947).

Sodium is not an inhibitor in all platinum oxide catalysts. A catalyst with the composition $Na_2O\cdot2PtO_2\cdot6H_2O$ was judged to be more active than Adam's catalyst for nuclear hydrogenation of compounds like aceto-phenone, where 1,4- or 1,6-addition involving both the carbonyl and ring is possible (Theilacker and Drössler, 1954).

Strong Acids

Small amounts of strong acids (Brown et al., 1936) often have marked influence on platinum oxide catalysts, perhaps through interaction with the sodium component. Attempts to reduce 2-benzylcyclopentanone over platinum oxide in methanol failed but, when the methanol was acidified with a little concentrated hydrochloric acid, four to five moles of hydrogen were rapidly absorbed, affording a mixture of cis-hexahydrobenzylcyclopentanol and a hydrocarbon, probably hexahydrobenzylcyclopentane (Phillips and Mentha, 1956). Similarly, traces of hydrochloric acid had a remarkable effect on the reduction of 2-isopropylidene-4-hydroxycoumaran-3-one (I) over platinum oxide in ethanol. Without hydrochloric acid, a 98% yield of the dihydro compound (II) was obtained. In alcohol containing 3 drops of hydrochloric acid, the dihydro compound absorbed five moles of hydrogen to give III. Attempts to reduce the aromatic ring without hydrochloric acid resulted in opening of the heterocyclic ring (Shriner and Witte, 1941).
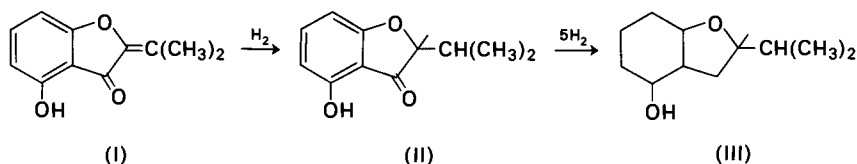
On occasion, weak acids may prove more advantageous than strong acids in counteracting the adverse effects of sodium. No reduction of p-acetamino-phenol took place over platinum oxide in neutral solution; in dilute hydro-chloric acid the ring was saturated but the hydroxyl group was lost as well, whereas in 96% alcohol containing 1% acetic acid the desired 4-acetamino-cyclohexanol was rapidly formed (Ferber and Brückner, 1939).

C. WATER

Water has a pronounced promoting effect in hydrogenation of aromatics over ruthenium catalysts. Table II shows the effect of water on the rate of reduction of benzoic acid over 5% ruthenium-on-carbon at 130°C and 2250 psig. In this system the rate increased steadily with each increase in water content of the system, leveling off after an approximate tenfold improvement at equal weights of water and substrate. Hexahydrobenzoic acid was used as a solvent to help disperse the liberated heat. A few experiments made without solvent established that water produced about the same increase in rate as with solvent.

Water also increases the rate of reduction somewhat over palladium and rhodium catalysts, but not nearly to the same extent as over ruthenium. Table III compares the rates of hydrogenation of benzoic acid over 5% palladium-, ruthenium-, and rhodium-on-carbon with and without water. Platinum catalysts were poisoned in these experiments. The comparisons are based on unequal weights of catalysts; reduction over rhodium was extremely fast under these conditions and less rhodium was used necessarily to obtain conveniently handled reductions (Rylander et al., 1963).

TABLE II

EFFECT OF WATER ON RATE OF HYDROGENATION OF BENZOIC ACID[a]

Water	Benzoic acid (gm reduced per minute)	
	Over 500 mg 5% Ru/C	Over 1500 mg 5% Ru/C
0	0.1	0.4
2	—	0.7
8	—	1.5
15	0.6	2.0
30	1.2	3.0
45	1.5	—
60	1.6	—

[a] Each experiment was carried out with 30 gm benzoic acid, 70 gm hexahydrobenzoic acid as solvent, and catalyst and water as noted, at 130°C and 2250 psig.

TABLE III
COMPARISON OF PLATINUM METALS IN BENZOIC ACID HYDROGENATION:
EFFECT OF WATER[a]

Catalyst	Amount (mg)	Benzoic acid (gm reduced per minute)[b]	
		No water present	15 gm water present
5% palladium-on-carbon	1500	0.3	0.4
5% ruthenium-on-carbon	1500	0.4	2.0
5% rhodium-on-carbon	500	2.0	3.0

[a] Each experiment was carried out with 30 gm benzoic acid and 70 gm hexahydrobenzoic acid at 130°C and 2250 psig.
[b] Approximate amounts. The data were abstracted from nonlinear rate curves.

D. SYNERGISM

Two platinum metals used together may display an enhanced activity in aromatic ring reduction. In hydrogenation of benzanthracene, a platinum oxide catalyst containing 1–2% of palladium added during the preparation was considerably more active than catalysts prepared from the same platinum but containing no palladium (Fieser and Hershberg, 1937). Hydrogenation of 1,2,3,4-tetrahydroacridine in methanol over palladium–platinum-on-carbon catalyst readily gave octahydroacridine, whereas no reduction occurred over palladium-on-carbon and was very slow over platinum-on-carbon (Hayashi and Nagao, 1964). A number of aromatic compounds were reduced over a rhodium-platinum oxide catalyst in acetic acid solution (Nishimura, 1960). This mixed catalyst was said to be more active in general than either platinum or palladium oxides, and was especially effective where hydrogenolysis of substituents was to be avoided (Nishimura, 1961; Nishimura and Taguchi, 1963). Synergistic effects have been noted in hydrogenation of aromatic systems over catalysts composed of mixtures of ruthenium and palladium or ruthenium and platinum (Rylander and Koch, 1965). Further examples of synergism are shown in Table VII.

II. PARTIAL REDUCTION OF AROMATIC RINGS

Partial reduction of a noncondensed aromatic ring is difficult to accomplish, inasmuch as the resulting olefin or diolefin is usually much more easily reduced than the original aromatic system. Nonetheless, in special situations reductions of this type may occur. Hydrogenation of the 4-styryl-pyrimidine derivative (IV) over platinum oxide occurred in two distinct

stages; the first two moles of hydrogen were absorbed in 10 minutes, the second two in 3 hours. The authors established that this sharp decline in rate was due to the nature of the intermediate, provisionally assigned the structure V, and not to deactivation of the catalyst. The olefinic double bond and the adjacent double bond in the benzenoid nucleus were assumed to absorb hydrogen as a conjugated system (Folkers and Johnson, 1933).

(IV)   (V)
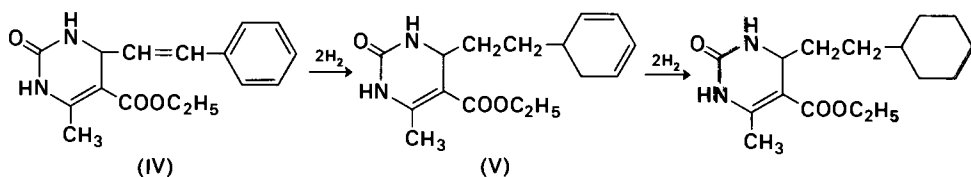
A similar simultaneous involvement of an external double bond and an aromatic nucleus might be inferred from the work of Shemin and Herbst (1939), who observed that, over fresh moist platinum oxide, α-acetamino-cinnamic acid absorbed four moles of hydrogen without a break in the rate curve. After the catalyst had been dried in a desiccator, a sharp decline in rate occurred after absorption of one mole.

An unusual partial ring reduction occurred during hydrogenation of (2.2)paracyclophane (VI) over platinum oxide in acetic acid. After four moles of hydrogen were consumed the rate decreased sharply, in some experiments coming to a complete stop. From analyses of the ultraviolet spectra and inspection of molecular models, the intermediate was assigned the non-conjugated structure (VII). Reduction of only one of the two aromatic rings of VI should give a product carrying a badly distorted benzene ring, and this material was in fact not obtainable; the products from VI after absorption of three moles of hydrogen were 62 % of VII and 20 % of unchanged starting material. In larger paracyclophanes the benzene rings could be hydrogenated independently of each other (Cram and Allinger, 1955).

(VI)   (VII)
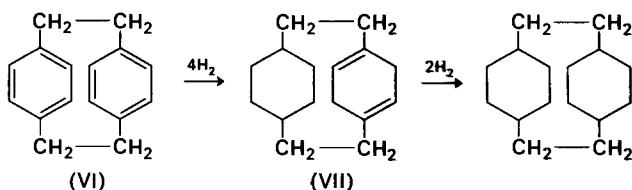
Terephthalic acid has been reduced in high yield to hexahydroterephthalic acid over 5 % palladium-on-carbon or 5 % ruthenium-on-carbon in water solvent at 180°C and 2500 psig (Dehm and Maury, 1959), or over rhodium oxide in acetic acid at 60–70°C and 1400 psig (Japanese Patent 27,245/64). Good yields of tetrahydroterephthalic acid may be obtained by carrying out the hydrogenation over ruthenium in alkaline media. A hydrogenation

carried out with 30 gm terephthalic acid, 10 ml water, 90 ml 2 N sodium hydroxide, and 1.5 gm 5% ruthenium-on-carbon at 140°C and 2250 psig afforded, after absorption of two equivalents of hydrogen, 3 gm Δ^1-tetrahydroterephthalic acid and 22 gm cis-Δ^2-tetrahydroterephthalic acid (Rylander and Rakoncza, 1964).
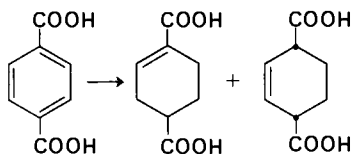
III. STRAINED RINGS

Most carbocyclic aromatic systems are inert, or essentially so, to reduction over palladium catalysts under mild conditions, but exceptions exist. The facile reduction of certain aromatics over palladium has been attributed to a strained ring system. The fused tricyclic aromatic compound (VIII) was readily reduced over palladium-on-carbon in ethanol at room temperature and pressure, whereas the similar compound (IX) was completely inert. Other attempts to detect strain in these ring systems by differences in reactivity, reflecting a decrease in benzene resonance stabilization, were unavailing (Rapoport and Pasky, 1956). Similarly, X was readily reduced
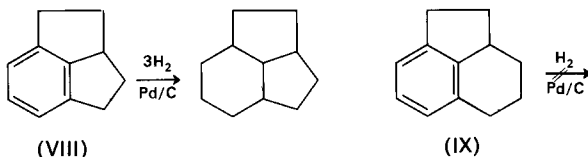
over 5% palladium-on-carbon in methanol, whereas the less strained compound (XI) was completely inert. Compound X unlike compound VIII or IX, did not display normal aromatic properties (Rapoport and Smolinsky, 1960).
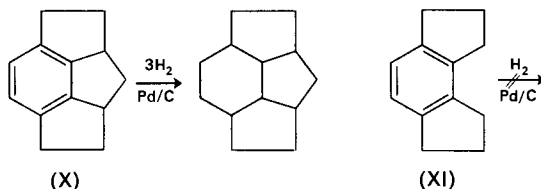
IV. SELECTIVE HYDROGENATION

Compared to most functional groups, the aromatic ring is reduced with relative difficulty. Examples of survival of the aromatic system abound,

but selective reductions in the converse sense are much rarer. Preferential reduction of an aromatic nucleus may depend on some structural feature of the molecule, rendering the usually more easily reduced function inaccessible to approach by the catalyst. In suitably structured molecules, even the nitro group has remained unchanged during reduction of an aromatic system. A slow hydrogenation of XII over 30% palladium-on-carbon in acetic acid afforded XIII. On the other hand, hydrogenation of XIV, in which the nitro group is slightly less hindered, resulted only in reduction of the nitro function (Young and Snyder, 1961).

(XII) R = —C$_2$H$_5$; (XIV) R = —CH$_3$ (XIII) R = —C$_2$H$_5$
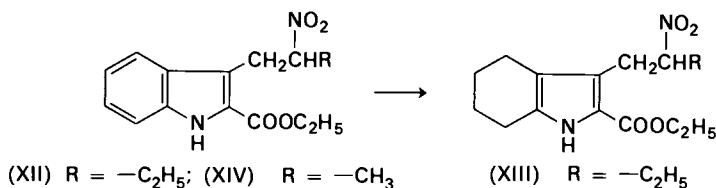
An interesting example of preferential ring reduction in the presence of a normally easily reduced function is the conversion of 2-methoxyphenyl-acetone (XV) to the corresponding saturated *cis*-ketone (XVI). The hydrogenation was carried out with 16 gm XV in 30 ml acetic acid over 5 gm 5% rhodium-on-alumina. After 10 hours hydrogen absorption ceased, and XVI was recovered by distillation in 78% yield. In methanol the reduction was less selective and the carbonyl function was partly reduced as well (Cantor and Tarbell, 1964). This paper also describes the use of rhodium-on-alumina for reduction of benzofurans.

(XV)   (XVI)
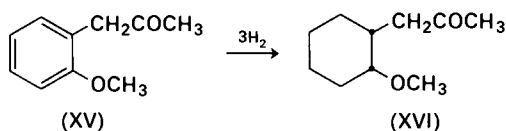
POLYPHENYL COMPOUNDS

Selective hydrogenation of only one phenyl ring in a compound containing several may sometimes be achieved with unexpected ease. For instance, almost quantitative yields of phenylcyclohexylacetic acid (XVIII) were obtained on half-hydrogenation of diphenylacetic acid (XVII) in acetic acid over platinum oxide (Smith *et al.*, 1949). The excellent selectivity obtained despite a near identity in rate for the first and second stages of the hydrogenation (rate ratio = 0.95). Evidently diphenylacetic acid was much more strongly absorbed on the catalyst than phenylcyclohexylacetic acid. Half-hydrogenation of benzilic acid (XIX), on the other hand, was not nearly so selective, the product being a mixture of 17.5% benzilic acid, 17.5% dicyclohexylglycolic acid (XXI), and 65% phenylcyclohexylglycolic acid (XX).

Kinetic analysis indicated that benzilic acid was absorbed on the catalyst 4.6 times more readily than phenylcyclohexylglycolic acid (Smith *et al.*, 1952).

(XVII)   R = H   (XVIII)   R = H   (XXI)   R = OH
(XIX)   R = OH   (XX)   R = OH
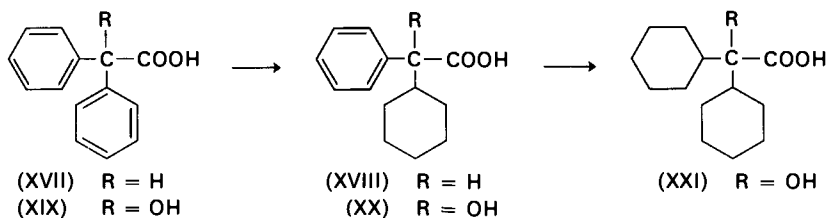
In certain compounds excellent yields of partially hydrogenated products are obtained automatically, and in fact it may be found impossible to achieve saturation of both rings. Hydrogenation of XXII as the dihydrochloride over platinum oxide at 55–60°C and 30 psig afforded XXIII in 94% yield (Zaugg *et al.*, 1958). Efforts to saturate both rings were unavailing, a result attributed to partial poisoning of the catalyst and not to the geometry of the system (Freifelder, 1964); reduction of both rings proceeded readily when the substrate was the quaternary methosulfate derivative instead of the dihydrochloride. Rhodium was less sensitive than platinum to the poisoning effect of the basic nitrogen atom.

(XXII)   (XXIII)
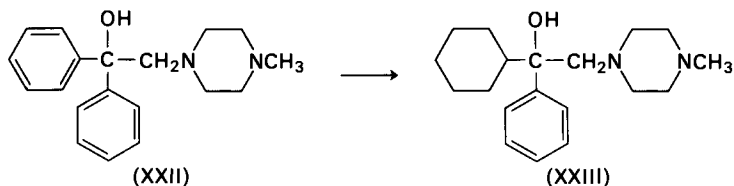
The effect that geometry may have on the selectivity of reduction seems clearer in compounds of the type of XXIV than in the examples previously mentioned. Hydrogenation of XXIV over platinum oxide in acetic acid stopped spontaneously after absorption of the three moles of hydrogen to give XXV in excellent yield. The ring reduced was assumed to be that lying *trans* to the substituents in the 2- and 3-positions, inasmuch as that ring could be most easily accommodated on the catalyst surface. A methyl substituent ($R = CH_3$) completely prevented hydrogenation by blocking adsorption of either ring. Nor could reduction of an *ortho*-biphenylene derivative be achieved, as both aromatic rings are held perpendicular to the cyclopropane ring and close approach to the catalyst surface is prevented (Baltzly *et al.*, 1961).

(XXIV)   R = H   (XXV)   R = H
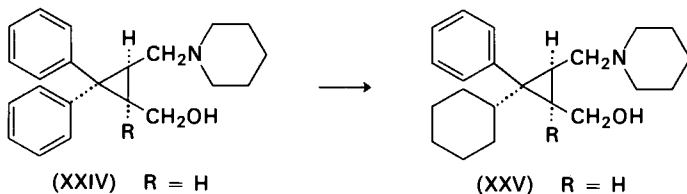
Effect of Catalyst

The data of Tables IV and V, related to the selectivity of hydrogenation of biphenyl and diphenylmethane, show a marked influence of catalyst (Rylander and Steele, 1965). Palladium is without question the best catalyst for conversion of biphenyl to cyclohexylbenzene; the other catalysts always produce products with the simultaneous presence of large amounts of starting material and dicyclohexyl. Selectivity depends somewhat on the solvent, and over palladium was greater in cyclohexane than in acetic acid.

TABLE IV

SELECTIVE HYDROGENATION OF BIPHENYL[a]

Catalyst	mg	Solvent	Rate (ml H_2 per min)	Biphenyl (mole %)	Cyclohexyl-benzene (mole %)	Bicyclo-hexyl (mole %)
5% Pd/C	600	Acetic acid	71	10	87	3
		Cyclohexane	52	3	97	0
5% Pt/C	600	Acetic acid[b]	—	—	—	—
		Cyclohexane	210	12	56	32
5% Rh/C	600	Acetic acid	496	15	58	27
		Cyclohexane	203	21	43	36
5% Ru/C	600	Acetic acid[c]	97	36	31	33
		Cyclohexane	78	35	34	31
5% Rh/Al$_2$O$_3$	600	Acetic acid	229	29	61	10
15% Ir/C	300	Cyclohexane	220	40	37	23

[a] All experiments carried out at 100°C and 1000 psig with 5–10 gm substrate in 25 ml solvent.
[b] Poisoned.
[c] Plus 10 ml water in the ruthenium reductions to increase the rate.

TABLE V

HYDROGENATION OF DIPHENYLMETHANE[a]

Catalyst	mg	Temp.	Rate (ml H_2 per min)	Diphenyl-methane (mole %)	Cyclohexyl-phenyl-methane (mole %)	Dicyclo-hexyl-methane (mole %)	H_2 (moles)
5% Pd/C	600	119	16	26	66	8	2.46
5% Pt/C	600	102	115	18	62	20	3.06
5% Rh/C	600	87	425	18	39	43	3.75
5% Rh/C[b]	300	35	90	54	34	12	1.74
PtO$_2$	200	32	450	34	47	19	2.55

[a] Experiments carried out at 1000 psig with 10 ml substrate in 25 ml acetic acid.
[b] With no solvent and 25 ml substrate.

Diphenylmethane is reduced with less selectivity than biphenyl; all partial reductions produced products with considerable quantities of both diphenyl-methane and fully saturated material (Table V). A brief excursion into the effect of pressure between atmospheric and 1000 psig and of temperature between 32° and 100°C over 5% rhodium-on-carbon revealed that selectivity was relatively little changed in this range of reaction conditions. The selectivity obtained with platinum oxide was less than that reported by earlier workers, who concluded from analyses based on distillation that essentially pure phenylcyclohexylmethane was formed by half-hydrogenation of diphenylmethane (Smith *et al.*, 1949).

V. REDUCTION OF BENZYL COMPOUNDS

Reduction of benzyl compounds carrying oxygen or nitrogen functions may yield one of several products, depending in large part on the catalyst used. Hydrogenolysis without ring saturation occurs readily over palladium catalysts (Hartung and Simonoff, 1953), although with certain compounds the aromatic system may be reduced as well (Phillips and Chatterjee, 1958).

X = —OH, —OR, —OCOR, —NH₂, —NHR, etc.
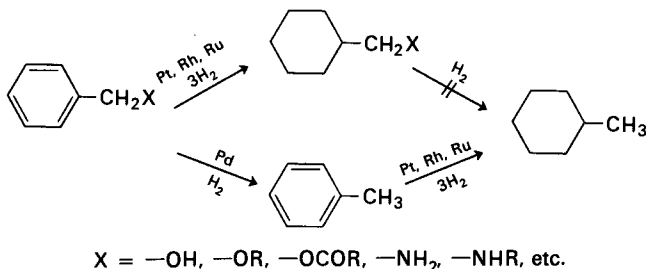
Ring saturation without hydrogenolysis may be achieved over platinum, or preferably rhodium or ruthenium, catalysts. Hydrogenolysis with ring reduction is accomplished best in two stages, hydrogenolysis followed by ring saturation, but not by the reverse sequence inasmuch as the cyclohexyl derivatives are resistant to hydrogenolysis.

A. RUTHENIUM

Reductions of aromatic rings over ruthenium are generally carried out at elevated pressures. Hydrogenation of 60 gm acetophenone over 0.6 gm ruthenium dioxide at 100°C and 1000 psig was complete in 1 hour and afforded 1-cyclohexylethanol in 88% yield (Freifelder *et al.*, 1964). Cyclo-hexyl-α,ω-glycols were obtained in high yield by reduction of the corresponding phenylglycols over ruthenium dioxide in ethanol at 80–120°C and

1000–2000 psig (Arnold, 1951). A solution of 82.6 gm *l*-ephedrine (XXVI) in 250 ml absolute ethanol was reduced to XXVII without change in rotation over 1.6 gm ruthenium dioxide at 1200 psig and 90°C in 40 minutes (Freifelder and Stone, 1958). Hydrogenation over palladium black was accompanied by reversal of rotation and, over platinum oxide, *l*-cyclohexylisopropyl-methylamine was formed. The smooth reduction of *l*-ephedrine over ruthenium is also of interest, in that the molecule is a β-phenylamine, a type of structure frequently saturated only with difficulty (Freifelder and Stone, 1958).

(XXVI)   (XXVII)
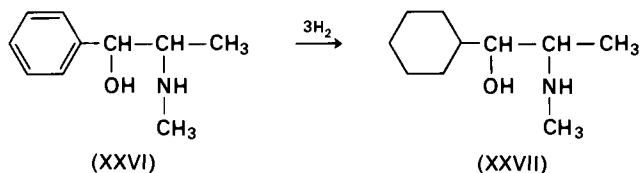
B. PLATINUM

Platinum catalysts have been used to achieve hydrogenolysis of a benzyl function without saturation of the aromatic ring (Hartung and Simonoff, 1953), but in many cases ring saturation may occur subsequently, con-comitantly, or preferentially. An attempt to effect debenzylation of XXVIII over platinum oxide in 50% aqueous ethanol containing hydrochloric acid failed; the reduction took an unexpected course, and only XXIX was produced (Grogan *et al.*, 1964).

(XXVIII)   (XXIX)
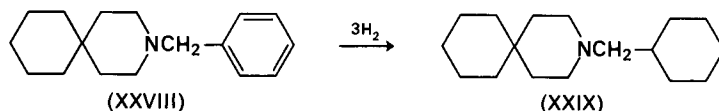
Similarly, hydrogenolysis was negligible during reduction of *p*-amino-methylbenzoic acid over platinum oxide in acetic acid at 60°C; a nearly quantitative yield of the saturated amino acid was obtained (Levine and Sedlecky, 1959).

Benzyl oxygen functions may also be retained under appropriate condi-tions during ring saturation over platinum. Benzyl alcohol and methyl-phenylcarbinol, compounds that readily undergo complete hydrogenolysis over palladium, were converted to the corresponding saturated carbinols in nearly quantitative yield by hydrogenation over prereduced platinum oxide in the presence of a trace of acetic acid. As the amount of acetic acid was increased, hydrogenolysis increased until the saturated hydrocarbon was the main product (Nishimura, 1959). Reduction of α,α'-dihydroxy-*p*-xylene over platinum black in isopropanol containing a small amount of acetic acid at 1400 psig gave 1,4-dihyroxymethylcyclohexane in 74% yield

(Japanese Patent 4747/65). Hydrogenolysis must ordinarily precede ring saturation if hydrogenolysis is to occur. When the two reactions take place at nearly equal rates, mixtures are formed. Hydrogenation of either aceto-phenone-o-carboxylic acid or 3-methylphthalide over platinum oxide in acetic acid gave the same mixture consisting of 60% XXX and 40% XXXI (Kolsaker, 1962). (The reduction of these compounds is discussed further in the chapter on hydrogenation of ketones.)
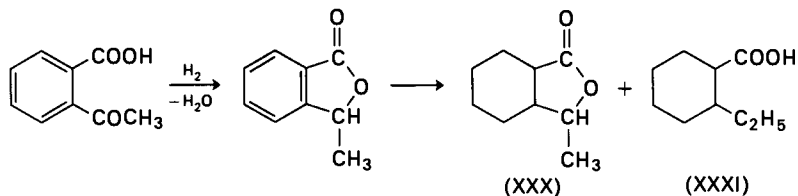
An interesting rearrangement leading to dodecahydrocarbazole (XXXIII) occurred during reduction of the complex benzyl alcohol (XXXII) over platinum oxide in acetic acid. The catalyst and hydrogen were apparently incidental to the rearrangement itself, which could be brought about by dilute acetic acid (Witkop, 1950).
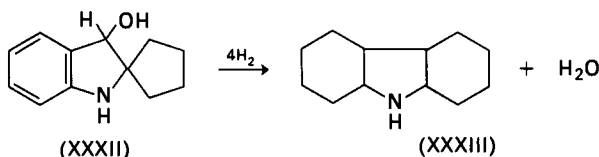
C. RHODIUM

Rhodium makes a very useful catalyst for reduction under mild conditions of α-substituted benzyl alcohols and ethers to the corresponding cyclohexyl derivatives. Stocker (1962) recommends this catalyst for establishing the configurations of the cyclohexyl counterparts of the many ring-substituted mandelic and atrolactic acids for which configurations are known, and for the general synthesis of the cyclohexyl compounds themselves. A typical reduction employed 7.60 gm DL-mandelic acid, 1.5 gm 5% rhodium-on-alumina, 40 ml absolute methanol, and 0.5 ml glacial acetic acid. Theoretical hydrogen was absorbed in 90 minutes. Concentration on a rotary evaporator afforded sharp melting DL-hexahydromandelic acid in 98.6% yield without recrystallization. Racemization does not accompany hydrogenation; D-mandelic acid afforded D-hexahydromandelic acid in 94% yield. The small amount of acetic acid employed in these reductions was reported to have a marked accelerating effect on the rate, a point subsequently confirmed

(Rakoncza, 1964). The technique is also applicable to diols; excellent yields of *meso*- and *dl*-2,3-dicyclohexyl-2,3-butanediol were obtained by hydrogenation of the corresponding diphenyldiol (Stocker, 1964). Oddly, unsatisfactory results—perhaps due to formation of cyclohexanecarboxaldehyde (Nishimura and Hama, 1966)—were obtained in reduction of benzyl alcohol (Stocker, 1962), although this substrate afforded quantitative yields of cyclohexylcarbinol over platinum oxide (Nishimura, 1959). Galantay (1963) obtained pure *cis*- and *trans*-cyclohexylcyclohexane-1,2-diol by reduction of the corresponding *cis*- and *trans*-1-phenylcylohexane-1,2-diol over 5% rhodium-on-alumina in aqueous suspension.

VI. FUSED RINGS

Fused rings seem to be reduced largely stepwise, one ring at a time. Good yields of intermediate products frequently may be obtained if the reduction is interrupted at the appropriate point. Exceptions exist, however. Reduction of dibenzofuran over platinum oxide in acetic acid gave at the halfway point only a mixture of starting material and perhydrodibenzofuran (Bradley, 1937); various intermediate products may be obtained by hydrogenation over nickel (Jones and Lindsey, 1950) or·palladium or rhodium (Steele, 1966) catalysts.

Hydrogenation of complex fused ring systems may take place at various rings concurrently and independently (Fieser and Hershberg, 1938), and special techniques are sometimes required to achieve satisfactory yields of intermediate products. In hydrogenation of dibenz(a, h)anthracene (XXXIV) over platinum oxide in 2,2,4-trimethylpentane-acetic acid reasonable quantities of the 1,2,3,4-tetrahydro derivative could be obtained only by carrying out the reduction in small portions (8 gm XXXIV in 400-mg portions) and combining the portions. Exhaustive hydrogenation gave XXXV with only the central ring unreduced (Lijinsky, 1961).

(XXXIV)   (XXXV)
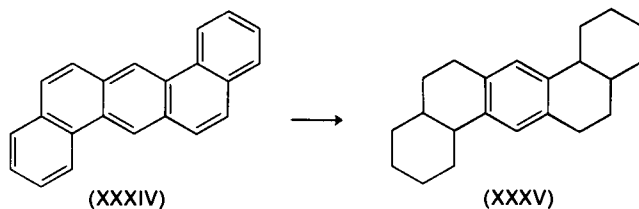
CATALYST

A comparison of platinum metals for hydrogenation of naphthalene dissolved in cyclohexane established the following order of decreasing

activity on a weight of metal basis: 5% rhodium- > 5% platinum- > 15% iridium- > 5% palladium-on-carbon. The reduction carried out at 1000 psig and 115–120°C proceeded predominantly stepwise: naphthalene → tetralin → decalin (see Weitkamp, 1966). Under these conditions, palladium-catalyzed reductions stopped spontaneously at the tetralin stage. Decalin obtained by reduction with platinum, iridium, and rhodium had 74%, 88%, and 90%, respectively, of the *cis* isomer (Rylander and Steele, 1965). Rhodium and ruthenium catalysts were about four times as active as 5% palladium-on-carbon for reduction of 9-methylcarbazole to *N*-methyldodecahydrocarbazole at 500 psig and 150–200°C (Dressler and Baum, 1961). Ruthenium-on-alumina in dioxane at 1350 psig (cold pressure) and 145°C smoothly reduced one ring of the Diels–Alder adduct of maleic acid and anthracene, whereas Raney nickel was nonselective (Kolobielski, 1963).

It appears that in general, despite the wide spread and successful use of platinum oxide, rhodium or ruthenium catalysts are the best suited of the platinum metals for complete or partial reduction of fused ring systems.

VII. STEREOCHEMISTRY

Hydrogenation of disubstituted aromatics under mild conditions gives mainly saturated *cis* isomers (Burwell, 1957), as if all the hydrogen had been added to one side of the molecule (Linstead *et al.*, 1942). Under vigorous conditions the fully hydrogenated products may be isomerized, and the resulting mixtures do not reflect the course of the original saturation. Some *trans* isomers are usually produced even under the mildest conditions. Their formation is frequently accounted for by total or partial desorption and re-adsorption in a new orientation of some partially hydrogenated intermediate (Hartog and Zwietering, 1963; Siegel *et al.*, 1962, 1963).

The distribution of stereoisomers obtained on hydrogenation of aromatics depends in large measure on the substituents; the *cis-trans* isomer ratio in the methylcyclohexanols resulting from hydrogenation of cresols is, for instance, quite different from that in dimethylcyclohexanes derived by hydrogenation of xylenes. The stereoisomer distribution also depends on the catalyst and operating conditions. In the following sections, the influence of some of these variables is examined with the xylenes as model substrates (Rylander and Steele, 1962).

A. EFFECT OF METAL

Table VI gives the percentage of *trans* isomer in the dimethylcyclohexanes resulting from hydrogenation of *o*-, *m*-, and *p*-xylenes. With each xylene,

TABLE VI
EFFECT OF METAL IN HYDROGENATION OF XYLENES[a]

Catalyst	Xylene	Rate (ml H_2/min)	Percent trans-dimethylcyclohexane
5% Rh/C	ortho	1400	10.8
5% Ru/C	ortho	875	7.4
5% Rh/C	meta	590	26.3
5% Ru/C	meta	115	15.5
5% Rh/C	para	2330	36.4
5% Ru/C	para	745	30.3

[a] Each experiment was carried out with 50 ml substrate and 300 mg catalyst, at 100°C and 1000 psig.

rhodium forms more trans isomer than ruthenium. The percentage of trans isomer generally agrees with that obtained by low pressure hydrogenation over platinum oxide at 85°C, which for o-, m-, and p-xylene was 12.7%, 19.0%, and 33.4%, respectively (Schuetz and Caswell, 1962). Under the conditions used to obtain the data of Table VI, 5% platinum-on-carbon gave a rate of less than 10 ml H_2/min for each xylene.

B. EFFECT OF TWO CATALYTIC METALS

Table VII compares the rates of hydrogenation and the percentages of trans isomer obtained in hydrogenation of xylenes over rhodium-, ruthenium-, platinum-, and palladium-on-carbon and various combinations of these metals coprecipitated-on-carbon. Most noteworthy are the exceedingly fast rates obtained with coprecipitated rhodium–ruthenium and rhodium–platinum. These unusually fast rates were attributed to the use of two metals together, although it was recognized that the preparations of the catalysts were necessarily different in each case. Despite synergistic effects on rate, the trans isomer content was about that expected from the most active metals. Rhodium–ruthenium gave a percentage of trans isomer in excess of that expected, but this may have been due to inadequate temperature control in this very fast reaction. The only hydrogenation made with palladium was at 160°C, the lowest temperature at which a convenient rate could be obtained.

Other workers (Hartog and Zwietering, 1963) have found the percent of trans-1,2-dimethylcylohexane obtained in hydrogenation at 25°C of o-xylene over a mixture of 0.5 gm 5% ruthenium-on-carbon and 1.5 gm 5% palladium-on-carbon to be larger (18.9%) than that obtained over ruthenium-on-carbon alone (7.6%). Under these conditions the palladium catalysts

TABLE VII

EFFECT OF TWO CATALYTIC METALS[a]

Catalyst (300 mg)	Xylene (50 ml)	Rate (ml H_2/min)	Percent trans-dimethylcyclohexane
5% Rh/C	para	2330	36.4
5% Ru/C	para	745	30.3
5% Pt/C	para	10	—
5% Pd/C[b]	para	100	52.7
2.5% Rh, 2.5% Ru/C	para	7800	44.6
2.5% Rh, 2.5% Pt/C	para	3960	35.5
2.5% Rh, 2.5% Pd/C	para	225	35.0
2.5% Rh, 2.5% Pt/C	meta	1100	22.6
2.5% Rh, 2.5% Pt/C	ortho	2045	8.6

[a] Each experiment (except with 5% Pd/C) carried out at 1000 psig and 100°C.
[b] Experiment carried out at 1000 psig and 160°C.

was insufficient to cause by itself measurable hydrogenation of the o-xylene. The influence of palladium was attributed to its role in reducing intermediate olefins, mainly 1,2-dimethylcyclohexene, which desorbed from the ruthenium catalyst. Hydrogenation of 1,2-dimethylcyclohexene over palladium affords 75.6% trans-1,2-dimethylcyclohexane.

C. EFFECT OF METAL CONCENTRATION

The effect of metal concentration on the percentage of trans isomer in the dimethylcylohexanes derived by hydrogenation of the xylenes is shown in Table VIII. The percentage of trans isomer increases considerably with an

TABLE VIII

EFFECT OF METAL CONCENTRATION IN HYDROGENATION OF XYLENES [a]

Catalyst	Xylene (50 ml)	Percent trans-dimethylcyclohexane
(300 mg) 5% Rh/C	ortho	10.8
(300 mg) 30% Rh/C	ortho	18.7
(300 mg) 5% Rh/C	para	36.4
(300 mg) 30% Rh/C	para	48.9
(50 mg) 30% Rh/C	para	47.0
(300 mg) 5% Rh/C	meta	26.3
(300 mg) 30% Rh/C	meta	23.0

[a] All experiments carried out at 100°C and 1000 psig.

increase in metal concentration in 1,2- and 1,4-dimethylcylohexane. The encompassing generality, for xylenes at least, is that increasing the concentration of metal in the catalyst increases the percentage of the more stable isomer. The observed effects of increasing the concentration of metal on the carrier are not caused by an increase in amount of metal in the reaction; 15 mg metal on a 30% rhodium-on-carbon gives almost the same percentage of trans-1,4-dimethylcyclohexane as 90 mg metal, but much different than 15 mg metal on a 5% rhodium-on-carbon catalyst.

D. EFFECT OF PRESSURE

The effect of pressure on the percentage of trans-dimethylcyclohexanes over rhodium-on-carbon at 100°C is small. Over the pressure range 1–70 atm the percentage of trans isomer varied at most a few percent. A detailed study of the effect of pressure over the range 0.25–300 atm was made, using reduced platinum oxide in acetic acid. Here, too, the pressure dependence was rather small, but the observed changes were useful nonetheless in elucidating the mechanism of hydrogenation (Siegel et al., 1962).

E. EFFECT OF CATALYST CARRIER

Table IX shows the percentage of trans-dimethylcyclohexanes obtained by hydrogenation of the xylenes over rhodium- and ruthenium-on-carbon,

TABLE IX
EFFECT OF CATALYST CARRIER IN HYDROGENATION OF XYLENES[a]

Catalyst	Percent trans isomer in dimethylcyclohexane		
	1,2-Dimethyl	1,3-Dimethyl	1,4-Dimethyl
5% Rh/C	6.5	15.6	22.7
5% Ru/C	3.0	9.3	23.8
5% Rh/kieselguhr	7.1	19.7	31.9
5% Ru/kieselguhr	6.0	—	27.0
5% Rh/SrCO$_3$	8.0	23.8	25.0
5% Ru/SrCO$_3$	4.3	11.8	31.8
5% Rh/BaCO$_3$	15.8	30.3	30.3
5% Ru/BaCO$_3$	3.6	15.7	27.6
5% Rh/BaSO$_4$	14.2	18.2	34.5
5% Ru/BaSO$_4$	5.2	14.4	—
5% Rh/Al$_2$O$_3$	8.0	27.8	29.5
5% Ru/Al$_2$O$_3$	9.7	14.7	29.4

[a] All experiments carried out at 50 psig initial pressure and room temperature.

-kieselguhr, -strontium carbonate, -barium carbonate, -barium sulfate, and
-alumina (Rylander *et al.*, 1965); with a few exceptions, rhodium tends to
produce more *trans*-dimethylcyclohexanes than ruthenium. Without excep-
tion, carbon-supported catalysts give less *trans* isomers than noncarbon
supports.

F. EFFECT OF WATER

The *trans* isomer content of dimethylcyclohexanes may be decreased
appreciably in certain cases by carrying out hydrogenation of xylenes in
the presence of water. Comparative results for hydrogenations at 50 psig
and room temperature are shown in Table X. Some sharp decreases in the
percentages of *trans* isomers occurred, but the effect is limited and its
magnitude depends both on the substrate and on the catalyst. At 100°C and
1000 psig, water had very little effect on the isomer distribution. Water may
change the isomer content by altering the tendency of olefinic intermediates
to desorb from the carbon support.

TABLE X
EFFECT OF WATER IN HYDROGENATION OF XYLENES[a]

Catalyst	Water	Percent *trans* isomer in dimethylcyclohexane		
		1,2-Dimethyl	1,3-Dimethyl	1,4-Dimethyl
5% Rh/C	No	6.5	15.6	22.7
	Yes	5.4	17.5	9.4
5% Ru/C	No	3.0	9.3	23.8
	Yes	<0.5	<0.5	23.8

[a] All experiments carried out at 50 psig initial pressure and room temperature. Water volume =
xylene volume.

G. EFFECT OF TEMPERATURE

Table XI shows the effect of temperature on the percentage of *trans*-
dimethylcyclohexane formed in hydrogenation of *p*-xylene over rhodium-on-
carbon (Rylander and Steele, 1962) and over platinum oxide (Schuetz and
Caswell, 1962). The percentage of *trans* isomer shows a marked dependence
on temperature; proper selection of temperature seems to be the best single
way of controlling isomer distribution, aside from choice of catalyst.
The percentage of *trans* isomers derived from hydrogenation of *o*-xylene

and *m*-xylene also increased with increasing temperature (Schuetz and Caswell, 1962).

TABLE XI

EFFECT OF TEMPERATURE IN HYDROGENATION OF *p*-XYLENE[a]

Catalyst	Temperature (°C)	Percent *trans* isomer
(600 mg) 5 % Rh/C	15	13.8
(300 mg) 5 % Rh/C	100	34.6
(300 mg) 5 % Rh/C	160	43.9
(200 mg) PtO$_2$[b]	36	24.5
(200 mg) PtO$_2$[b]	85	33.4

[a] Reductions over rhodium carried out at 100°C and 1000 psig without solvent. Reductions over platinum oxide carried out at low pressure in acetic acid.

[b] Data of Schuetz and Caswell (1962).

REFERENCES

Adams, R., and Marshall, J. R., *J. Am. Chem. Soc.* **50**, 1970 (1928).

Arnold, H. W., U.S. Patent 2,555,912, June 5, 1951.

Baker, R. H., and Schuetz, R. D., *J. Am. Chem. Soc.* **69**, 1250 (1947).

Baltzly, R., Mehta, N. B., Russell, P. B., Brooks, R. E., Grivsky, E. M., and Steinberg, A. M., *J. Org. Chem.* **26**, 3669 (1961).

Bradley, C. W., *Iowa State Coll. J. Sci.* **12**, 108 (1937).

Broadbent, H. S., Allred, E. L., Pendleton, L., and Whittle, C. W., *J. Am. Chem. Soc.* **82**, 189 (1960).

Brown, J. H., Durand, H. W., and Marvel, C. S., *J. Am. Chem. Soc.* **58**, 1594 (1936).

Burger, A., and Mosettig, E., *J. Am. Chem. Soc.*, **58**, 1857 (1936).

Burwell, R. L., Jr., *Chem. Rev.* **57**, 895 (1957).

Cantor, S. E., and Tarbell, D. S., *J. Am. Chem. Soc.* **86**, 2902 (1964).

Cram, D. J., and Allinger, N. L., *J. Am. Chem. Soc.* **77**, 6289 (1955).

Dehm, H. C., and Maury, L. G., U.S. Patent 2,888,484, May 26, 1959.

Dressler, H., and Baum, M. E., *J. Org. Chem.* **26**, 102 (1961).

Ferber, E., and Brückner, H., *Chem. Ber.* **72B**, 995 (1939).

Fieser, L. F., and Hershberg, E. B., *J. Am. Chem. Soc.* **59**, 2502 (1937).

Fieser, L. F., and Hershberg, E. B., *J. Am. Chem. Soc.* **60**, 940 (1938).

Folkers, K., and Johnson, T. B., *J. Am. Chem. Soc.* **55**, 1140 (1933).

Freedman, L. D., and Doak, G. O., *J. Org. Chem.* **24**, 638 (1959).

Freedman, L. D., Doak, G. O., and Petit, E. L., *J. Am. Chem. Soc.* **77**, 4262 (1955).

Freifelder, M., *J. Org. Chem.* **26**, 1835 (1961).

Freifelder, M., *J. Org. Chem.* **29**, 979 (1964).

Freifelder, M., and Stone, G. R., *J. Am. Chem. Soc.* **80**, 5270 (1958).

Freifelder, M., Anderson, T., Ng, Y. H., and Papendick, V., *J. Pharm. Sci.* **53**, 967 (1964).

Galantay, E., *Tetrahedron* **19**, 319 (1963).

Grogan, C. H., Geschickter, C. F., and Rice, L. M., *J. Med. Chem.* **7**, 78 (1964).

Hartog, F., and Zwietering, P., *J. Catalysis* **2**, 79 (1963).
Hartung, W. H., and Simonoff, R., *Org. Reactions* **7**, 263 (1953).
Hayashi, E., and Nagao, T., *Yakugaku Zasshi* **84**(2), 198 (1964).
Jones, J. I., and Lindsey, A. S., *J. Chem. Soc.* p. 1836 (1950).
Keenan, C. W., Giesemann, B. W., and Smith, H. A., *J. Am. Chem. Soc.* **76**, 229 (1954).
Kolobielski, M., *J. Org. Chem.* **28**, 1883 (1963).
Kolsaker, P., *Acta Chem. Scand.* **16**, 1056 (1962).
Levine, M., and Sedlecky, R., *J. Org. Chem.* **24**, 115 (1959).
Lijinsky, W., *J. Org. Chem.* **26**, 3230 (1961).
Linstead, R. P., Doering, W. E., Davis, S. B., Levine, P., and Whetstone, R. R., *J. Am. Chem. Soc.* **64**, 1985 (1942).
Montgomery, J. B., Hoffmann, A. N., Glasebrook, A. L., and Thigpen, J. I., *Ind. Eng. Chem.* **50**, 313 (1958).
Nishimura, S., *Bull. Chem. Soc. Japan* **32**, 1155 (1959).
Nishimura, S., *Bull. Chem. Soc. Japan* **33**, 566 (1960).
Nishimura, S., *Bull. Chem. Soc. Japan* **34**, 32 (1961).
Nishimura, S., and Hama, M., *Bull. Chem. Soc. Japan*, **39**, 2467 (1966).
Nishimura, S., and Taguchi, H., *Bull. Chem. Soc. Japan* **36**, 353 (1963).
Phillips, A. P., and Mentha, J., *J. Am. Chem. Soc.* **78**, 140 (1956).
Phillips, D. D., and Chatterjee, D. N., *J. Am. Chem. Soc.* **80**, 4364 (1958).
Rakoncza, N., Unpublished observations, Engelhard Ind., 1964.
Rapoport, H., and Pasky, J. Z., *J. Am. Chem. Soc.* **78**, 3788 (1956).
Rapoport, H., and Smolinsky, G., *J. Am. Chem. Soc.* **82**, 1171 (1960).
Rylander, P. N., and Koch, J. H., Jr., U.S. Patent 3,177,258, April 6, 1965.
Rylander, P. N., and Rakoncza, N. F., U. S. Patent 3,163,679, Dec. 22, 1964.
Rylander, P. N., and Steele, D. R., *Engelhard Ind. Tech. Bull.* **3**, 91 (1962).
Rylander, P. N., and Steele, D. R., *Engelhard Ind. Tech. Bull.* **5**, 113 (1965).
Rylander, P. N., Rakoncza, N., Steele, D., and Bollinger, M., *Engelhard Ind. Tech. Bull.* **4**, 95 (1963).
Rylander, P. N., Kilroy, M., and Coven, V., *Engelhard Ind. Tech. Bull.* **6**, 11 (1965).
Schuetz, R. D., and Caswell, L. R., *J. Org. Chem.* **27**, 486 (1962).
Shemin, D., and Herbst, R. M., *J. Am. Chem. Soc.* **61**, 2471 (1939).
Shriner, R. L., and Witte, M., *J. Am. Chem. Soc.* **62**, 2134 (1941).
Siegel, S., Smith, G. V., Dmuchovsky, B., Dubbell, D., and W. Halpern, W., *J. Am. Chem. Soc.* **84**, 31 6 (1962).
Siegel, S., Ku, V., and Halpern, W., *J. Catalysis* **2**, 348 (1963).
Smith, H. A., Alderman, D. M., Jr., Shacklett, C. D., and Welch, C. M., *J. Am. Chem. Soc.* **71**, 3772 (1949).
Smith, H. A., Shacklett, C. D., and Welch, C. M., *J. Am. Chem. Soc.* **74**, 4534 (1952).
Steele, D. R., Unpublished observations, Engelhard Ind., 1966.
Stocker, J. H., *J. Org. Chem.* **27**, 2288 (1962)
Stocker, J. H., *J. Org. Chem.* **29**, 3593 (1964).
Theilacker, W., and Drössler, H. G., *Chem. Ber.* **87**, 1676 (1954).
Weitkamp, A. W., *J. Catalysis*, **6**, 431 (1966).
Weygand, C., and Werner, A., *Chem. Ber.* **71B**, 2469 (1938).
Witkop, B., *J. Am. Chem. Soc.* **72**, 614 (1950).
Young, D. V., and Snyder, H. R., *J. Am. Chem. Soc.* **83**, 3160 (1961).
Zaugg, H. E., Michaels, R. J., Glenn, H. J., Swett, L. R., Freifelder, M., Stone, G. R., and Weston, A. W., *J. Am. Chem. Soc.* **80**, 2763 (1958).

19

Phenols and Phenyl Ethers

Phenols and phenyl ethers are considered together because, except for ketone formation from phenols, they behave similarly on catalytic hydrogenation. All products of reduction may be considered to be derived by variants of four reactions. This chapter is organized around these four classifications:

Hydrogenolysis without ring reduction (Section III):

$$\text{C}_6\text{H}_5\text{--OR} \;+\; \text{H}_2 \;\longrightarrow\; \text{C}_6\text{H}_6 \;+\; \text{ROH}$$
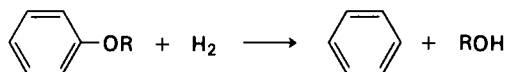
Partial ring reduction (Section IV):

$$\text{C}_6\text{H}_5\text{--OH} \;+\; 2\text{H}_2 \;\longrightarrow\; \text{C}_6\text{H}_{10}{=}\text{O}$$
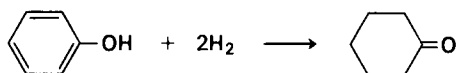
Ring reduction without hydrogenolysis (Section V):

$$\text{C}_6\text{H}_5\text{--OR} \;+\; 3\text{H}_2 \;\longrightarrow\; \text{C}_6\text{H}_{11}\text{--OR}$$
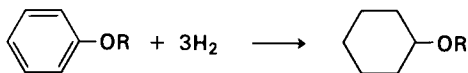
Ring reduction with hydrogenolysis (Section VI):

$$\text{C}_6\text{H}_5\text{--OR} \;+\; 4\text{H}_2 \;\longrightarrow\; \text{C}_6\text{H}_{12} \;+\; \text{ROH}$$
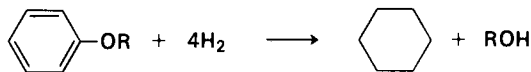
I. PLATINUM METALS

A comparison has been made of the activities of 5% iridium-, palladium-, platinum-, rhodium-, and ruthenium-on-carbon for hydrogenation of phenol in several solvents (Rylander and Steele, 1962). The rates are tabulated in

Table I. With a proper choice of solvent, each of these catalysts reduced phenol at a satisfactory rate.

TABLE I

HYDROGENATION OF PHENOL IN VARIOUS SOLVENTS[a]

Catalyst	Rate of hydrogenation (ml H_2 absorbed/min) in:				
	No Solvent	Water	Acetic acid	Dimethyl-formamide	Methanol
Ir	250	340	25	<10	38
Pd	85	55	50	<10	<10
Pt	450	290	160[p]	<10	<10
Rh	470	400	110[p]	<10	450
Ru	315	260	30	<10	170

[a] 300 mg 5% metal-on-carbon, 100°C, 1000 psig; 50 ml substrate without solvent, or 25 ml substrate and 25 ml solvent; [p] = initial rate only, rate gradually declined.

Phenols and phenyl ethers are often reduced at a faster rate over platinum catalysts in acidic solution than in neutral or alkaline solution. However, the reverse condition may well apply when ruthenium catalysts are used. Comparative rate data for the hydrogenation of several compounds over 5% platinum-on-carbon and 5% ruthenium-on-carbon in acidic, neutral, and basic solution are given in Table II (Rylander and Kreidl, 1965).

In hydrogenation of phenols the rate is usually of only secondary importance for, as will be seen, the products vary greatly with the catalysts and conditions.

TABLE II

EFFECT OF pH ON HYDROGENATION RATE [a]

Substrate	Ml H_2 absorbed/min					
	HCl (0.1 N)		H$_2$O		NaOH (0.1 N)	
	5% Pt/C	5% Ru/C	5% Pt/C	5% Ru/C	5% Pt/C	5% Ru/C
Phenol	21.5	0.0	4.6	2.0	3.0	7.5
Anisole	3.8	0.0	1.0	0.9	0.0	10.0
1,4-Dimethoxybenzene	2.6	0.0	5.0	1.3	0.0	7.0

[a] Hydrogenations carried out at 50 psig, 25°C, with 50 ml solvent, 0.1 mole of substrate, and 300 mg catalyst.

II. EFFECT OF CATALYST AND TEMPERATURE ON STEREOCHEMISTRY

With cresols as model substrates, the effect of catalyst on the stereochemistry of hydrogenation was examined; the results are shown in Table III. Except for hydrogenation of p-cresol by ruthenium-on-carbon, the results follow the rule that for each cresol the percentage of stable isomer increases with the catalyst in the order, rhodium-on-carbon, ruthenium-on-carbon, and platinum oxide—the same order observed in hydrogenation of the

TABLE III

HYDROGENATION OF CRESOLS TO METHYLCYCLOHEXANOLS[a]

Substrate	Percent more stable isomer			
	5% Rh/C (300 mg)	5% Ru/C (300 mg)	5% Pt/C[b] (300 mg)	PtO$_2$[c] (500 mg)
o-Cresol (trans)	48	49	—	61
m-Cresol (cis)	61	63	—	75*
				73**
p-Cresol (trans)	51	42	—	63*
		40		60**

[a] Temperature: 100°C; pressure: 1000 psig.
[b] Only low conversions were obtained with these substrates and the analytical values were consequently unreliable.
[c] * = Acid (pH = 4.2); ** = Alkaline (pH = 8.0). These values were the pH of the solution obtained by suspending 500 mg PtO$_2$ in 10 ml water.

TABLE IV

HYDROGENATION OF CRESOLS: EFFECT OF TEMPERATURE[a]

Substrate	Temp. (°C)	Catalyst	Percent more stable isomer
p-Cresol	26	500 mg PtO$_2$	58 (trans)
	52	500 mg PtO$_2$	61
	100	500 mg PtO$_2$	63
	30	300 mg 5% Rh/C	39 (trans)
	53	300 mg 5% Rh/C	41
	100	300 mg 5% Rh/C	51
m-Cresol	31	300 mg 5% Rh/C	79 (cis)
	52	300 mg 5% Rh/C	74
	100	300 mg 5% Rh/C	62

[a] Pressure = 1000 psig.

methylcyclohexanones. With the same exception, the percentage of stable isomer increases with each catalyst in the order, *ortho-*, *para-*, *meta*-cresol (Rylander and Steele, 1963). The presence of alkali in platinum oxide can at times markedly alter the course of a hydrogenation (Dart and Henbest, 1959). Platinum oxide catalysts showing either acid or alkaline reactions when suspended in water were tested, as noted in Table III, but apparently the course of cresol reduction is almost insensitive to this type of change.

Observations have also been made on the effect of temperature on isomer distribution in products arising from reduction of cresols (Table IV). Between room temperature and 100°C, the percentage of *trans* isomer increases slightly when platinum oxide is the catalyst. With rhodium, the dependence is somewhat greater. The generality that might be applied to these data is that the percentage of *trans* isomer increases with temperature.

III. HYDROGENOLYSIS WITHOUT RING REDUCTION

Loss of oxygen without some reduction of the aromatic ring is rarely observed in catalytic hydrogenation of phenols and phenyl ethers under mild conditions. Loss of oxygen, followed by further hydrogenation, offers one route, but not necessarily an important one, by which saturated products may be formed. For instance, reduction of resorcinol over 5% palladium-on-carbon affords 2.4% phenol, when the reduction is interrupted after absorption of one equivalent of hydrogen (Rylander and Himelstein, 1964). Similarly, small amounts of phenol were found in an uncompleted reduction of *p*-methoxyphenol in ethanol over 5% rhodium-on-carbon, 5% palladium-on-carbon, and platinum oxide (Himelstein, 1964). Hydrogenolyses of this type may be fairly common side-reactions, but they will ordinarily pass unobserved unless the reductions are interrupted.

An unusual example is found in the selective hydrogenolysis of the 1-methoxy group when I is reduced over platinum oxide in acetic acid. The reduction stopped after absorption of three equivalents of hydrogen, and II was isolated in excellent yield. This product undoubtedly arose by oxidation during work-up of an uncharacterized primary hydrogenation product (Cohen and Taylor, 1963).

(I)   (II)
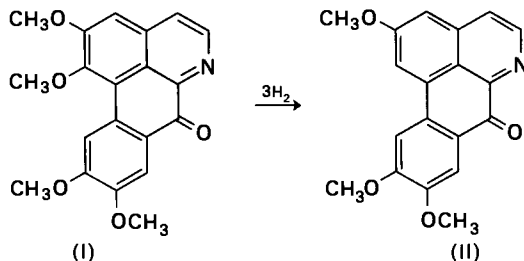
TABLE V

HYDROGENATION OF RESORCINOL IN ETHANOL[a]

	Moles of H_2 absorbed (nominal)	Mole % in product							
		Resorcinol	Dihydro-resorcinol	Hydroxy-cyclo-hexanone	Phenol	Cyclo-hexanone	Cyclo-hexenol	Cyclo-hexanediol	Cyclo-hexanol
5% Pd/C	1	48.5	1.3	1.4	2.4	35.8	5.8	3.1	1.2
5% Pt/C	1	62.5	0	9.4	0	1.4	0	9.8	16.8
5% Rh/C	1	61.3	0	0	0	3.9	16.7	14.0	4.1
5% Pd/C	2	26.8	0	0	0	33.5	36.0	3.7	0
5% Pt/C	2	31.3	0	8.4	0	3.6	0	16.1	40.6
5% Rh/C	2	28.2	0	0	0	4.3	5.7	50.5	11.3
5% Pd/C	>3	0	0	0	0	0	0	20.5	79.5
5% Pt/C	>3	0	0	2.3	0	2.8	0	18.7	76.2
5% Rh/C	>3	0	0	0	0	0	0	70.0	30.0

[a] Each experiment was made with 1000 mg catalyst, 50 ml 95% ethanol, and 0.1 mole of resorcinol, at 65°C and 50 psig. These are nine separate experiments and not three, interrupted at various points.

IV. PARTIAL RING REDUCTION

Phenols may give several partially reduced materials. For instance, partial hydrogenation of resorcinol in ethanol gave a mixture of phenol, dihydroresorcinol, hydroxycyclohexanone, cyclohexanone, and cyclohexenol, in addition to the saturated products, cyclohexanol and cyclohexanediol. The composition of the final products and intermediate mixtures depends greatly on the catalyst, as shown by selected comparisons in Table V.

The grossly different percentage of intermediate products obtained over various catalysts is related to the relative adsorbability of these products on the catalyst. An equimolar mixture of resorcinol and cyclohexanone in ethanol was competitively hydrogenated over several catalysts, and the hydrogenation stopped at various stages; the results are shown in Table VI.

TABLE VI

COMPETITIVE HYDROGENATION OF RESORCINOL AND CYCLOHEXANONE[a]

Catalyst	Change in number of moles ($\times$ 10)			
	Resorcinol	Cyclohexanone	Cyclohexanol	Cyclohexanediol
5% Pd/C	−0.3	+0.3	0	0
5% Pt/C	0	−0.72	+0.72	0
5% Rh/C	−0.28	−0.14	+0.24	+0.18

[a] Each experiment used 0.1 mole of resorcinol, 0.1 mole of cyclohexanone, 50 ml 95% ethanol, and 1000 mg catalyst at 65°C and 50 psig initial pressure.

It is clear that over palladium-on-carbon resorcinol is reduced to the exclusion of cyclohexanone, while over platinum-on-carbon the reverse is true. No such marked preference for substrate is observed in reduction over rhodium-on-carbon (Rylander and Himelstein, 1964). A kinetic study of the hydrogenation of hydroxybenzenes suggests that, although ketones are formed in the hydrogenation of phenols, they need not necessarily be intermediates in formation of cyclohexanols (Smith and Stump, 1961).

A. KETONES

Good yields of ketones may be obtained by selective catalytic hydrogenation of phenols:
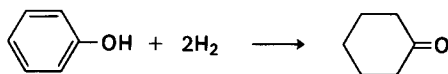
Alternatively or additionally, the ketone may be formed in a disproportiona-
tion of unchanged phenol and alcohol formed by saturation of the phenol:
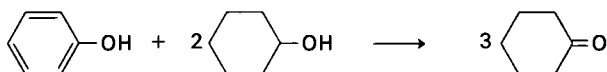
The yield of ketone formed in selective hydrogenation of phenols depends
on the relative rate of reduction in competition of the phenol to the ketone,
and further reduction of the ketone to the alcohol. The yield of ketone
obtainable by disproportionation depends on the thermodynamics of the
process; it has been estimated that with suitable catalysts the ketone may
be formed in yields of about 50% (Zil'berman, 1954).

1. Palladium

Palladium has proved to be a useful catalyst for hydrogenation of phenols
to ketones. Cyclohexanone can be formed in high yield directly from phenol
by hydrogenation in the presence of palladium-on-carbon catalysts. The
reduction is very sensitive to the effects of sodium in solution, and catalysts
promoted by 1000–7000 ppm of sodium are preferred. The sodium may be
added as sodium salts to the reaction mixture. Too much sodium promotes
cyclohexanol formation. A reduction at 215°C and 70 psig, with 0.03 gm
sodium as sodium carbonate per 1000 gm phenol, gave after 150 minutes
a product containing 91.5% cyclohexanone and 8% cyclohexanol; with
2 gm sodium per 1000 gm phenol, the composition was only 19.5% cyclo-
hexanone and 80% cyclohexanol (Duggan et al., 1963).

Other workers have reduced phenol to cyclohexanone in dilute hydro-
chloric acid over a palladium hydroxide-on-barium sulfate catalyst washed
free of residual barium carbonate by very dilute acetic acid (Kuhn and
Haas, 1958). Cyclohexanone may also be formed in excellent yield by vapor
phase hydrogenation of phenol over 0.5% palladium-on-alumina at
140–190°C (British Patent 890,095), or by hydrogenation of molten phenol
over 5% palladium-on-carbon (Joris and Vitrone, 1958). Hydrogenation
of 1,8-dihydroxynaphthalene over palladium-on-carbon afforded 8-hydroxy-
1-tetralone (Kaye and Matthews, 1963).

A surprisingly facile reduction and dehydrohalogenation of a highly
hindered phenol was observed by Hart and Cassis (1951). 4-Chloro-2,6-di-*t*-
butylphenol was reduced to 2,6-di-*t*-butylcyclohexanone by palladium
chloride-on-carbon at room temperature and 750 psig.
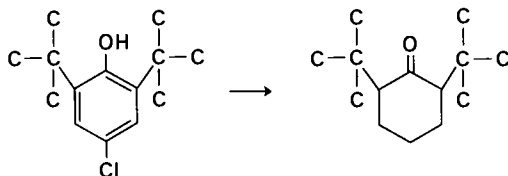
Catalytic hydrogenation of 2,4-dimethylphenol over palladium-on-carbon led directly to 2,4-dimethylcyclohexanone containing 7% *cis* and 93% *trans* isomers (Johnson *et al.*, 1964).
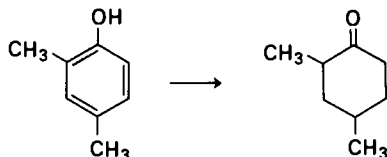
Palladium-on-carbon was considered the preferred catalyst for simultaneous hydrogenation of the cinnamic double bond and conversion of the resorcinol unit of III to the saturated diketone (IV), an intermediate for cyclodehydration to 3-ketophenanthrenes. The reduction required a concomitant hydrolysis of the phenol acetate and phenol lactone without

(III)   (IV)
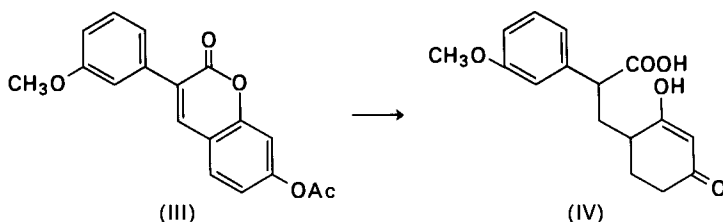
hydrogenation of the methoxyphenyl part of the molecule. The transformation was achieved successfully by carrying out the reduction at 80°C over 10% palladium-on-carbon in 1% sodium hydroxide solution containing 3.1 equivalents of base. A high catalyst loading was used in these reductions, 8 gm catalyst for 0.0275 mole of coumarin (III) (Walker, 1958).

2. Rhodium

Under certain conditions rhodium catalysts have given good yields of ketones from phenols, but satisfactory results seem to be quite sensitive to the reduction medium. Dihydroresorcinol cannot be detected in reduction of resorcinol in ethanol over 5% rhodium-on-carbon (Table V) but, if the reduction is carried out in aqueous sodium hydroxide, dihydroresorcinol is obtained in 87% yield (Smith and Stump, 1961). When palladium-on-carbon is used instead of rhodium the yields are only 50–60% (Esch and Schaeffer, 1960).
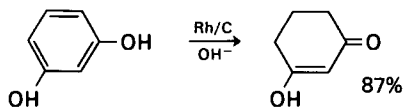
Excellent yields of decalols can be obtained by reduction of α- or β-naphthol over 5% rhodium-on-alumina in methanol or ethanol, but in acetic acid solvent the major product is decalone, obtainable in 70% yield. The high percentage of decalones was attributed to deactivation of the catalyst during the reduction. When a fresh sample of catalyst was added the reduction went rapidly and completely to the decalols (Meyers *et al.*, 1964).
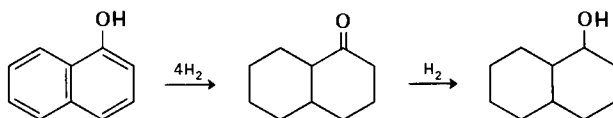
B. Reductive Amination of Phenols

Phenols may be reductively aminated by carrying out the reduction in the presence of ammonia or an amine. Presumably the phenol is reduced to a ketone, which then undergoes a normal reductive amination. An example is the preparation of dicyclohexylamine from reduction over palladium of an equimolar mixture of phenol and aniline at pressures below 100 psig (Belgian Patent 627,187).
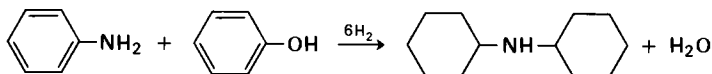
V. RING SATURATION WITHOUT HYDROGENOLYSIS

Reduction of phenols and phenyl ethers to the corresponding cyclohexanols and cyclohexyl ethers can nowadays usually be accomplished with very little hydrogenolysis. The preferred catalysts are rhodium and ruthenium, and to a lesser extent palladium; iridium and platinum will in general give less satisfactory results.

A. Palladium

Very few phenols or phenyl ethers can be reduced to the saturated derivatives at a satisfactory rate over palladium catalysts, unless elevated temperatures and/or pressures are employed. An interesting exception is found in the work of Schrecker and Hartwell (1953), who reduced dehydroanhydropicropodophyllin (V) at atmospheric pressure to the 5,6,7,8-tetrahydrolactone (VI) in 80% yield in acetic acid solvent and in the presence of 10% palladium-on-carbon.

(V)   (VI)
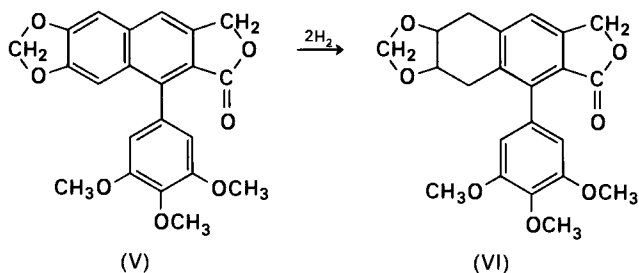
Attempts to hydrogenate β-apopicropodophyllin with platinum oxide in ethanol or acetic acid (in the presence or absence of perchloric acid) or with palladium-on-barium sulfate all failed; hydrogen uptake was rapid, however, with palladium-on-carbon in acetic acid to give a 73% yield of the above reduction product (VI).

Phenol saturations over palladium are usually carried out under fairly vigorous conditions, often with very satisfactory results. High pressure apparently favors hydrogenation relative to hydrogenolysis. Reduction of ethyl p-hydroxybenzoate at 43 psig in ethyl acetate with palladium-on-strontium carbon as catalyst gave 44% of ethyl 4-hydroxycyclohexanecarboxylate, 16% of ethyl cyclohexanecarboxylate, and 27% of unchanged material. Reduction at high pressure (pressure not stated) gave a quantitative yield of the 4-hydroxy ester (Levin and Pendergrass, 1947). Palladium-on-strontium carbonate in dioxane gives a quantitative yield of ethyl 4-hydroxy-cyclohexanecarboxylate at 150–180°C and 2250 psig (Martin and Robinson, 1943). The dioxane must be pure, and the catalyst loses activity when heated under hydrogen without stirring; the reduction should therefore be continuous. Di-(4-hydroxycyclohexyl)-methane was isolated in 74% yield after hydrogenation of 4,4′-dihydroxydiphenylmethane over 2% palladium-on-strontium carbonate at 165°C and 1600 psig (Novello and Christy, 1951). Reduction of 4-t-butylphenol over 5% palladium-on-barium carbonate at 175°C and 1500–1800 psig proceeded rapidly to give almost quantitative yields of 4-t-butylcyclohexanol containing 56% cis isomer (Somerville and Theimer, 1960). Pyrogallol was reduced to cis,cis-cyclohexane-1,2,3-triol in 70–77% yields over 2% palladium-on-strontium carbonate in dioxane at 2400 psig and 75–80°C. The authors noted that the catalyst was readily inactivated by adventitious impurities. Inactivation occurred regularly in a 2000 ml Aminco stainless steel bomb, but not in one of 500 ml capacity, even when the rates of heating were equalized and the same solutions and catalyst were used (Christian et al., 1951).

Palladium-on-carbon proved to be the best of the platinum metal catalysts for selective hydrogenation of p-phenylphenol to either phenylcyclohexanol or cyclohexylphenol (Rylander and Steele, 1965).
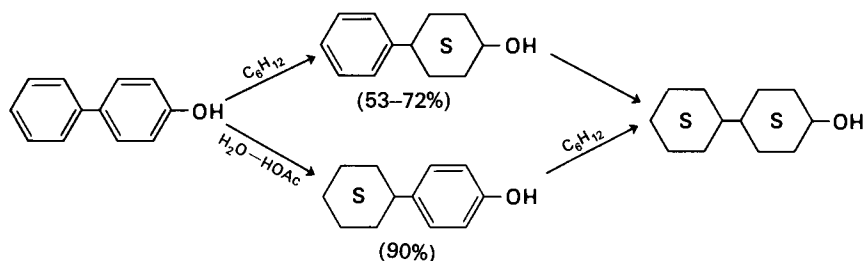
The major product was determined by the solvent. In water-acetic acid, p-cyclohexylphenol was formed in yields exceeding 90%; in cyclohexane, phenylcyclohexanol was formed in 53–72% yield. The reductions were carried out at 1000 psig and 125–130°C. The effect of solvent in this reduction may be viewed as arising from a change in the relative adsorbabilities of the rings on the catalyst surface. In the polar water-acetic acid system, it might be assumed that the phenolic ring is more strongly solvated and hence less readily adsorbed on the catalyst surface than in cyclohexane solvent. Conversely, cyclohexane favors solvation of the nonpolar phenyl ring, with the consequence that the phenolic ring is adsorbed preferentially.

B. RHODIUM

Rhodium catalysts will saturate phenols and phenyl ethers at room temperature and pressure, but better rates are obtained when more vigorous conditions are used. The usefulness of rhodium in reducing phenols and phenyl ethers without excessive hydrogenolysis is shown by the data of Table VII. The high yields of saturated product are all the more striking when compared with the extremely low yields obtained by reduction of platinum oxide under identical conditions. Phenol, catechol, resorcinol, and hydroquinone have also been reduced over 5% rhodium-on-carbon in water solvent at room temperature and pressure without measurable hydrogenolysis (Gilman and Cohn, 1957). Anomalous rate curves were obtained in reductions in water; the rate suddenly increased when the reduction was about $\frac{5}{6}$ complete, a phenomenon interpretable in terms of competition between the original substrate and intermediate hydrogenation products.

A typical low pressure hydrogenation of a phenol over rhodium may be illustrated by the work of Kaye and Matthews (1963) on the reduction of o-hydroxyacetophenone to 2-(1-hydroxyethyl)cyclohexanol:
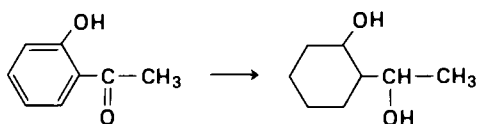
TABLE VII

EFFECT OF TEMPERATURE AND SUBSTRATE STRUCTURE ON HYDROGENOLYSIS[a]

| Substrate | Yield of corresponding cyclohexyl compound | | | |
| | Over PtO_2 | | Over 5% Rh/Al_2O_3 | |
	20°C	50°C	20°C	50°C
Anisole[b]	62	60	93	98
1,2-Dimethoxybenzene[b]	8	0	91	77
1,3-Dimethoxybenzene[b]	5	0	75	41
1,4-Dimethoxybenzene[b]	7	0	93	50
1,2,3-Trimethoxybenzene[b]	5	0	68	53
Phenol[c]	81	62	96	96
Catechol[c]	39	32	96	87
Resorcinol[c]	9	0	93	84
Hydroquinone[c]	4	0	71	79
Phloroglucinol[c]	72	36	—	—
Pyrogallol[c]	43	17	88	76

[a] Hydrogenations carried out at 50 psig initial pressure in glacial acetic acid. The yields were calculated from published absorption measurements, assuming that no difunctional molecule lost more than one substituent.

[b] Calculated from the data of Smith and Thompson (1957).

[c] Calculated from the data of Smith and Stump (1961).

This example is especially interesting in that both the phenolic hydroxyl and the readily cleaved benzylic hydroxyl (its formation prior to ring reduction is assumed as a major pathway) are retained. A mixture of 43.2 gm o-hydroxyacetophenone, 5 gm rhodium-on-alumina, and 20 ml 95% ethanol was reduced at 50°C and 50 psig until absorption ceased. The diol was isolated in 78% yield. Similar low pressure reductions were carried out with γ-3-hydroxyphenylbutyric acid, 8-hydroxy-1-tetralone, and 7-hydroxy-1-indanone. The success of reduction of γ-3-hydroxyphenylbutyric acid and subsequent oxidation of the product to 3-(3-carbomethoxypropyl)cyclohexanone depended on the purity of the starting material. The overall yield was 75% starting with a better quality substrate, and only 50% when a cruder material was used.

Several 3-hydroxy-4-alkylbenzoic acids were reduced with high stereospecificity to the all-cis isomers over 5% rhodium-on-alumina in acetic acid. The yield was excellent when R = t-butyl, but fair when R = methyl, ethyl, or isopropyl, apparently because of some hydrogenolysis (Noyce and Dolby, 1961).

$R = CH_3, C_2H_5,$ iso-C_3H_7, t-C_4H_9
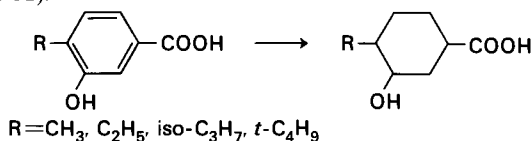
Reduction of *m*-methoxyphenol in 95% ethanol over 5% rhodium-on-alumina gave a 92% yield of 3-methoxycyclohexanol, which contained 45.5% *trans* and 54.5% *cis* isomers. In a second hydrogenation with a fresh batch of catalyst, the product was 60% *trans* isomer. Guaiacol on reduction over rhodium-on-alumina gave an impure product that required extensive purification [the material collected was 90.3% *cis*- and 9.7% *trans*-2-, methoxycyclohexanol (Eliel and Brett, 1963).]

Reductions under elevated pressures proceed more rapidly. High yields of *cis,cis*-1-decalol were obtained by reduction of 1-naphthol over 5% rhodium-on-carbon in ethanol at 1950 psig and room temperature; 30 gm catalyst was used for 72 gm naphthol, and the reduction was complete in an hour. Only about 3% of an impurity was found in the product.
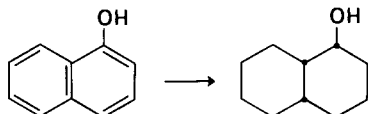
When the reduction was carried out at 60°C and 45 psig the product contained about 85% decalol, 5% decalin, and 10% 1-decalone as estimated by gas chromatography. Interruption of the reduction after absorption of two equivalents of hydrogen gave about 70% 5,6,7,8-tetrahydro-1-naphthol (Freifelder and Stone, 1964). Decalols have also been obtained by hydrogenation of 1-naphthol over platinum oxide but the yields are lower. Hydrogenation of 72 gm 1-naphthol in acetic acid in the presence of platinum oxide at low pressure gave 32 gm *cis,cis*-1-decalol, 5.5 gm decalin, and 19.3 gm mixed decalols. The total yield of decalols was 67% (Dauben *et al.*, 1954).

Rhodium-on-alumina in ethanol at 75°C and 2500 psig gave an all-*cis*-hexahydrogallic acid in 45–50% yield on hydrogenation of gallic acid. When water or dioxane was used as solvent, or when palladium- or ruthenium-on-carbon was used, relatively poor yields were obtained. The yield is said to depend on the activity of the rhodium catalyst (Burgstahler and Bithos, 1960). This procedure is a decided improvement over the previous two-step reduction—Raney nickel in base followed by platinum oxide in methanol, which gave 13–19% overall yields (Mayer *et al.*, 1955). Reduction of pyrogallol over rhodium-on-alumina at 3000 psig gave *cis,cis*-1,2,3-cyclohexanetriol in 62% yield (Burgstahler and Bithos, 1960). Ethyl 4-hydroxycyclohexylacetate was prepared in 83% yield by reduction of ethyl *p*-hydroxyphenylacetate over 5% rhodium-on-alumina in ethanol at 3000 psig and 40°C (Whitehead *et al.*, 1961). Extensive hydrogenolysis occurs when this compound is reduced over platinum catalysts.
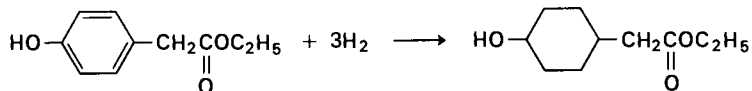
C. RUTHENIUM

Excellent results have been obtained in hydrogenation of phenols over ruthenium catalysts. Hydrogenolysis may be kept to a low level even with compounds where it occurs extensively over other catalysts. Satisfactory rates are obtained only if elevated pressures are used. The following examples illustrate the range of reaction conditions that has been employed and, when the comparisons have been made, contrast the results with other catalysts.

Ireland and Schiess (1963) reduced VII to the alcohol (VIII) and, without isolation, oxidized it to the ketone (IX) in 95% overall yield of crude product. The reduction was carried out by shaking 6.2 gm of the phenol and 0.62 gm ruthenium dioxide in 70 ml ethanol for 8 hours at 1500 psig and 50°C.

(VII)   (VIII)   (IX)
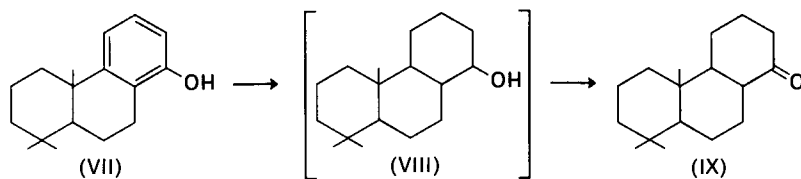
Ruthenium oxide at 1500 psig and 50°C proved to be a useful catalyst for reduction of X in ethanol solvent (Johnson et al., 1956). A single crystalline hydroxy acetate (XI) was isolated in over 50% yield. Hydrogenation over platinum oxide resulted in extensive hydrogenolysis.

(X)   (XI)
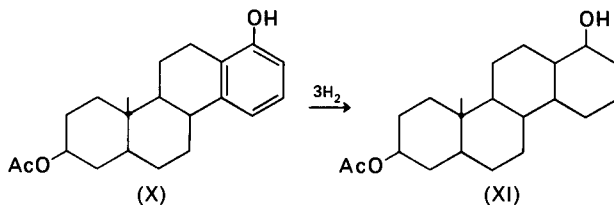
Reduction of the octahydrophenanthrene (XII) to XIII presented difficulty, as hydrogenolysis usually accompanied ring saturation. The problem was satisfactorily solved by reduction over 10% ruthenium-on-carbon at 15,000 psig and 125°C for 5 hours in methylcyclohexane solvent. Higher temperatures (150–225°C) or longer times gave extensive hydrogenolysis. Under the conditions cited ring saturation was completed with virtually no hydrogenolysis (Walton et al., 1956). This procedure proved superior to the use of palladium-on-strontium carbonate (Cornforth and Robinson, 1949).

(XII)   (XIII)
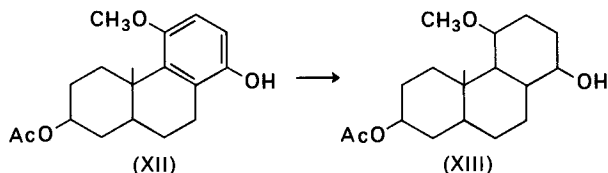
p-Hydroxybenzoic acid was reduced in high yield to 4-hydroxycyclo-hexanecarboxylic acid over 5% ruthenium-on-carbon in 90% aqueous ethanol at 145°C and 800 psig. Rhodium-on-carbon was poisoned under these conditions, palladium-on-carbon was insufficiently active, and platinum-on-carbon caused extensive hydrogenolysis (Rakoncza, 1962).
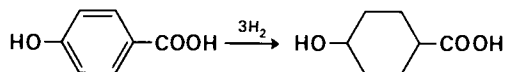
Hydrogenation of 2,6-bis(hydroxymethyl)-4-methylphenol in ethanol in the presence of ruthenium oxide at 1000–2500 psig gave a mixture of 2,6-bis(hydroxymethyl)-4-methylcyclohexanol, 2,4,6-trimethylcyclohexanol, and 2-hydroxymethyl-4, 6-dimethylcyclohexanol. The hydrogenolysis products predominated, but the oxygen loss was benzylic rather than phenolic (Frank, 1949). In the presence of ruthenium oxide, 100 gm 2-naphthol in ethanol was reduced at about 1000 psig and 90°C to give 98 gm *cis,cis*-2-decalol (Rodig and Ellis, 1961). Under roughly these same conditions, 5% rhodium-on-alumina was shown to be considerably more active than 5% ruthenium-on-carbon. A product analysis was not made in this comparative study (Gilman and Cohn, 1957).

VI. RING REDUCTION WITH HYDROGENOLYSIS

Extensive hydrogenolysis may occur during reduction of phenols and phenyl ethers, especially when platinum and, limited data suggest, iridium are used. Before the introduction of rhodium and ruthenium catalysts, hydrogenation of certain phenols without excessive hydrogenolysis offered a major challenge.

A. PLATINUM

The efficiency of platinum catalysts in promoting hydrogenolysis of phenols is well documented. 3-Methoxy-4-hydroxypropylbenzene was reduced to propylcyclohexane in acetic acid solvent in the presence of platinum (Gauthier, 1945). Diphenyl ethers undergo hydrogenolysis at room temperature and pressure in the presence of platinum oxide, giving cyclohexanols (Tomita and Uyeo, 1942). Extensive hydrogenolysis accompanied reduction of *p*-methoxyphenylacetic acid over platinum oxide; the principal product was cyclohexaneacetic acid (Ruggli *et al.*, 1941). Reduction of *p*-hydroxybenzoic acid over platinum oxide in water gave hexahydroben-

zoic acid in 75–80% yield. The remainder was identified as *trans*-4-hydroxy-cyclohexane-1-carboxylic acid. Less hydrogenolysis occurred with the *meta* isomer and still less with the *ortho* (Edson, 1934).

Hydrogenation of the phenol, N-acetyl-7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline, proceeded readily in acetic acid over platinum oxide. However, the reduction was accompanied by extensive hydrogenolysis of the hydroxyl group, and not more than 10% of N-acetyl-7-hydroxy-8-methyldecahydroisoquinoline was obtained. The ring junction had a *trans* configuration in this compound, but in the deoxy compound the configuration was *cis*. No reduction of the tetrahydroisoquinoline occurred at all over platinum oxide in any solvent, if the nitrogen were not first acetylated (Woodward and Doering, 1945).
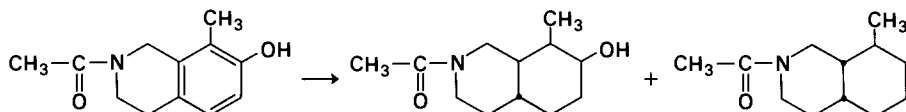
Only the hydrogenolysis product decahydronaphthoic acid (XIV) was obtained from total reduction of either 6-hydroxy-1-naphthoic acid (XV) or 6-hydroxy-1,2,3,4-tetrahydro-1-naphthoic acid (XVI) over platinum oxide in absolute alcohol containing 3 drops of alcoholic hydrogen chloride (Price *et al.*, 1947). Good yields of XVII may be obtained by partial reduction of XV over platinum catalysts. The hydrogenation of hydroxynaphthoic acids has been discussed at some length (Dauben *et al.*, 1951).
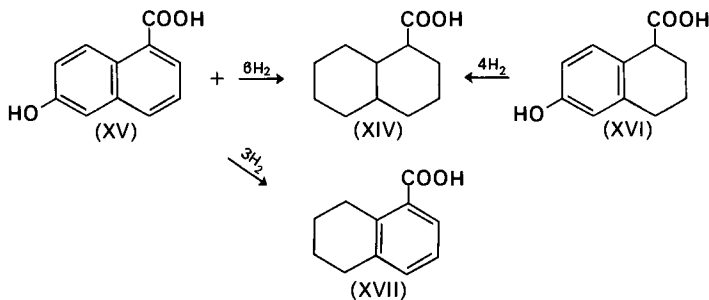
Success in reduction of a phenol was in one instance dependent on the preparation of the platinum oxide catalyst (Johnson *et al.*, 1956). Reduction of XVIII in acetic acid over platinum oxide, prepared according to the method of Adams *et al.* (1946), gave about 30% of a hydrogenolysis product plus two diols, isolated in 9% and 21% yields. The acetoxy phenol (XIX), however, resisted hydrogenation over this catalyst, but was readily reduced over platinum oxide prepared differently (Frampton *et al.*, 1951). About 18%

of the substrate suffered hydrogenolysis when this catalyst was used, but none did when ruthenium dioxide was used.
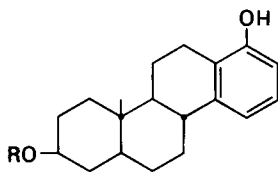
(XVIII) R = H
(XIX) R = CH₃CO

An interesting observation relating the extent of hydrogenolysis to the size of the batch has been made (Dauben *et al.*, 1952). Hydrogenolysis accompanying hydrogenation of 2-naphthol over platinum oxide in ether-acetic acid was less when the reduction was made on a smaller scale.

Temperature

An increase in temperature generally tends in the direction of increasing hydrogenolysis. A quantitative measure has been obtained of the effect of temperature on hydrogenolysis during reduction of several hydroxybenzenes (Smith and Stump, 1961) and several methoxybenzenes (Smith and Thompson, 1957) over platinum oxide and over 5% rhodium-on-alumina in acetic acid. Some examples from this work are given in Table VII. Encompassing generalities relating the extent of hydrogenolysis to substrate and catalyst are not evident, but the date suffice to indicate the magnitude of the change in percent hydrogenolysis to be expected over this temperature range.

B. IRIDIUM

Iridium catalysts have rarely been used for hydrogenation of phenols and derivatives. In hydrogenation of cresols and xylenols, iridium was comparable to and in some cases superior to platinum in promoting hydrogenolysis of the aryl–oxygen bond (Rylander and Steele, 1965a). For instance reduction of 2,5-dimethylphenol in isopropanol at 750 psig and 100°C gave 1,4-dimethylcyclohexane in 13% yield over 5% platinum-on-carbon, and in 60% yield over 5% iridium-on-carbon. During hydrogenation of *p*-phenylphenol over platinum, palladium, rhodium, ruthenium, and iridium, appreciable loss of oxygen occurred only over iridium and platinum catalysts (Rylander and Steele, 1965b). Iridium catalysts are evidently worthy of consideration when hydrogenolysis is a desired reaction.

C. PALLADIUM

Palladium catalysts may or may not give extensive hydrogenolysis, depending largely on the substrate. At one time palladium-on-strontium carbonate (Martin and Robinson, 1943) was preferred catalyst for hydrogenation of certain phenols when hydrogenolysis was to be avoided. On the other hand, reduction of other compounds, such as dihydroxybenzenes or methoxyphenols, over palladium catalyst is apt to be accompanied by extensive hydrogenolysis, especially at low pressures. Hydrogenolysis of resorcinol in ethanol over palladium-on-carbon was even more extensive than over platinum-on-carbon (Table V). Reduction of p-methoxyphenol over platinum oxide and over 5% palladium-on-carbon in ethanol at 65°C gave, respectively, only 8.4% and 9.4% yields of 4-methoxycyclohexanol, accompanied in each case by large amounts of cyclohexyl methyl ether and cyclohexanol (Himelstein, 1964).

D. ACID

Saturation of aromatic rings over platinum oxide (Brown *et al.*, 1936) and over platinum-on-carbon (Steele, 1966) has been shown to be catalyzed by small amounts of halogen acids, and so has the hydrogenolysis of hydroxy and alkoxy substituents. Efforts to increase the rate of ring saturation by addition of acids probably will also increase the extent of hydrogenolysis. Levin and Pendergrass (1947) found, in agreement with earlier workers, extensive hydrogenolysis during reduction over platinum oxide of *m*- and *p*-hydroxybenzoic acids and some derivatives; hydrogenolysis was increased by the presence of acetic acid or hydrochloric acid, but decreased by the presence of potassium hydroxide, which however, had an adverse effect on the rate of hydrogenation. Protection of the hydroxyl group by acetylation or methylation did not prevent hydrogenolysis. Hydrogenation of *N*-acetyl-*p*-aminophenol over platinum oxide in the presence of hydrochloric acid resulted in loss of hydroxyl, but in neutral alcohol at 60°C the product was a mixture of *cis*- and *trans*-4-acetaminocyclohexanol (Ferber and Brückner, 1939). Perhydrogenation of octahydro-9-phenanthrol and phenanthrones proved difficult because of hydrogenolysis, especially in acetic acid. The use of platinum in alcohol gave a slower hydrogenation, but with little elimination of oxygen (Linstead *et al.*, 1942).

The promoting effect of acids on hydrogenolysis may be put to good use when the deoxy product is desired. For instance, hydrogenation of tyrosine in 1 *N* hydrochloric acid over platinum oxide gave a mixture of 10% hexahydrotyrosine and 90% β-cyclohexylalanine (Karrer and Kehl, 1930). The yield of β-cyclohexylalanine was raised to 100% and a troublesome

separation eliminated by carrying out the reduction in 1.5–2.0 N hydrochloric acid and ethyl alcohol. Alcohol was used to prevent β-cyclohexylalanine hydrochloride from precipitating on the catalyst surface and diminishing its efficiency (Billman and Buehler, 1953).

$$HO-\underset{}{\bigcirc}-CH_2-\overset{NH_3{}^+Cl^-}{\underset{|}{C}H}-COOH + 4H_2 \longrightarrow \underset{}{\bigcirc}-CH_2-\overset{NH_3{}^+Cl^-}{\underset{|}{C}H}-COOH + H_2O$$
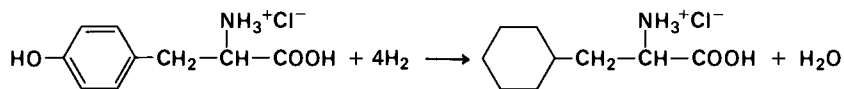
E. Substrate

The susceptibility of phenols to hydrogenolysis depends on their structure as well as the catalyst and conditions. Hydrogenolysis is favored by the presence of other hydroxy, alkoxy, or amino substituents. For instance, while reduction of anisole and phenetole over colloidal platinum in acetic acid gave chiefly the corresponding hexahydro derivatives, reduction of aminoanisole and aminophenetole led to cyclohexylamine (Skita and Rolfes, 1920). Reduction of m-aminophenol hydrochloride over platinum oxide in water afforded only the hydrogenolysis and coupling products, cyclohexylamine, dicyclohexylamine, and 3-cyclohexylaminocyclohexanol (Heckel and Adams, 1925).

A quantitive measure of the influence on hydrogenolysis of additional methoxy or hydroxy substituents is given in Table VII. The tabulated yields were calculated from published absorption measurements, assuming that no difunctional molecule lost more than one substituent. The actual yield of the corresponding disubstituted saturated derivative will be a little higher than that calculated in this way.

Dimethoxybenzenes and dihydroxybenzenes are very much more susceptible to hydrogenolysis over platinum oxide than anisole and phenol. The trihydroxybenzenes are more resistant to hydrogenolysis than dihydroxybenzenes, however. (The data of Table VII also show the great advantage of using rhodium catalysts when hydrogenolysis is to be avoided.)

Reduction of hexahydroxybenzene over palladium gave a 35% yield of crude inositol, accompanied by hydrogenolysis products ranging to cyclohexanetriols. The stable and available tetrahydroxybenzoquinone may be used as a starting material instead of the easily oxidized hexahydroxybenzene. At room temperature with a colloidal palladium catalyst, myo-inositol is the main product; palladium-on-carbon affords mainly cis-inositol (Angyal and McHugh, 1957).

Alkyl substituents in phenols evidently do not tend to promote hydrogenolysis and may actually have a stabilizing effect. Hydrogenation of o-cresol in acetic acid in the presence of platinum black, followed by saponification, gave an 82% yield of methylcyclohexanol, which contained 85%

of the *cis* isomer. A similar hydrogenation using platinum oxide gave an 86% yield of methylcyclohexanol with only 48% of the *cis* isomer (Hückel and Hubele, 1958). Only minor hydrogenolysis occurred in reduction of cresols without solvent over 5% platinum-on-carbon or platinum oxide (Rylander and Steele, 1963). Less than 5% of the substrate underwent hydrogenolysis when *o*-, *m*-, and *p*-cresols were reduced over 5% platinum-on-carbon in ethanol, acetic acid, or cyclohexane at 750 psig and 25–110°C (Steele, 1966).

F. ALKYL–OXYGEN BOND CLEAVAGE

Hydrogenation of phenyl alkyl ethers may be accompanied by cleavage of the alkyl–oxygen bond as well as the aryl–oxygen bond:
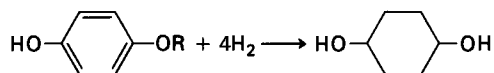
This reduction is not of importance except when some structural feature, such as R = benzyl, renders the O—R bond particularly labile. It has been observed, however, even when R = CH_3. Cyclohexanediol was formed in 5.3% yield during hydrogenation of *p*-methoxyphenol in ethanol over 5% rhodium-on-carbon at 65°C. No trace of the diol could be found when the catalyst was 5% palladium-on-carbon or platinum oxide (Himelstein, 1964).

REFERENCES

Adams, R., Voorhees, V., and Shriner, R. L., *In* "Organic Syntheses," Collected Vol. I, p. 463. Wiley, New York, 1946. (Gilman, H. and Blatt, A. H., ed.).
Angyal, S. J., and McHugh, D. J., *J. Chem. Soc.* p. 3682 (1957).
Billman, J. H., and Buehler, J. A., *Proc. Indiana Acad. Sci.* **63**, 120 (1953).
Brown, J. H., Durand, H. W., and Marvel, C. S., *J. Am. Chem. Soc.* **58**, 1594 (1936).
Burgstahler, A. W., and Bithos, Z. J., *J. Am. Chem. Soc.* **82**, 5466 (1960).
Christian, W. R., Gogek, C. J., and Purves, C. B., *Can. J. Chem.* **29**, 911 (1951).
Cohen, J., and Taylor, W. I., *J. Org. Chem.* **28**, 3567 (1963).
Cornforth, J. W., and Robinson, R., *J. Chem. Soc.* p. 1855 (1949).
Dart, M. C., and Henbest, H. B., *Nature* **183**, 817 (1959).
Dauben, W. G., Hiskey, C. F., and Markhart, A. H., Jr., *J. Am. Chem. Soc.* **73**, 1393 (1951).
Dauben, W. G., Hoerger, E., and Freeman, N. K., *J. Am. Chem. Soc.* **74**, 5206 (1952).
Dauben, W. G., Tweit, R. C., and Mannerskantz, C., *J. Am. Chem. Soc.* **76**, 4420 (1954).
Duggan, R. J., Murray, E. J., and Winstrom, L. O., U.S. Patent 3,076,810, Feb. 5, 1963.
Edson, N. L., *J. Soc. Chem. Ind.* (*London*) **53**, 138 (1934).
Eliel, E. L., and Brett, T. J., *J. Org. Chem.* **28**, 1923 (1963).
Esch, B., and Schaeffer, H. J., *J. Am. Pharm. Assoc. Sci. Ed.* **49**, 786 (1960).
Ferber, E., and Brückner, H., *Chem. Ber.* **72B**, 995 (1939).
Frampton, V. L., Edwards, J. D., Jr., and Henze, H. R., *J. Am. Chem. Soc.* **73**, 4432 (1951).

Frank, C. E., U.S. Patent 2,478,261, Aug. 9, 1949.

Freifelder, M., and Stone, G. R., *J. Pharm. Sci.* **53**, 1134 (1964).

Gauthier, B., *Ann. Chim. (Paris)* 11th series, **20**, 581 (1945).

Gilman, G., and Cohn, G., *Advan. Catalysis* **9**, 733 (1957).

Hart, H., and Cassis, F. A., Jr., *J. Am. Chem. Soc.* **73**, 3179 (1951).

Heckel, H., and Adams, R., *J. Am. Chem. Soc.* **47**, 1712 (1925).

Himelstein, N., Unpublished observations, Engelhard Ind., 1964.

Hückel, W., and Hubele, A., *Ann. Chem.* **613**, 27 (1958).

Ireland, R. E., and Schiess, P. W., *J. Org. Chem.* **28**, 6 (1963).

Johnson, F., Starkovsky, N. A., Paton, A. C., and Carlson, A. A., *J. Am. Chem. Soc.* **86**, 118 (1964).

Johnson, W. S., Rogier, E. R., and Ackerman, J., *J. Am. Chem. Soc.* **78**, 6322 (1956).

Joris, G. G., and Vitrone, J., Jr., U.S. Patents 2,829,163 and 2,829,166, April 1, 1958.

Karrer, P., and Kehl, W., *Helv. Chim. Acta* **13**, 50 (1930).

Kaye, I. A., and Matthews, R. S., *J. Org. Chem.* **28**, 325 (1963).

Kuhn, R., and Haas, H. J., *Ann. Chem.* **611**, 57 (1958).

Levin, R. H., and Pendergrass, J. H., *J. Am. Chem. Soc.* **69**, 2436 (1947).

Linstead, R. P., Whetstone, R. R., and Levine, P., *J. Am. Chem. Soc.* **64**, 2014 (1942).

Martin, R. H., and Robinson, R., *J. Chem. Soc.* p. 491 (1943).

Mayer, W., Bachmann, R., and Kraus, F., *Chem. Ber.* **88**, 316 (1955).

Meyers, A. I., Beverung, W., and Garcia-Munoz, G., *J. Org. Chem.* **29**, 3427 (1964).

Novello, F. C., and Christy, M. E., *J. Am. Chem. Soc.* **73**, 1267 (1951).

Noyce, D. S., and Dolby, L. J., *J. Org. Chem.* **26**, 1732 (1961).

Price, C. C., Enos, H. I., Jr., and Kaplan, W., *J. Am. Chem. Soc.* **69**, 2261 (1947).

Rakoncza, N., Unpublished observations, Engelhard Ind., 1962.

Rodig, O. R., and Ellis, L. C., *J. Org. Chem.* **26**, 2197 (1961).

Ruggli, P., Leupin, O., and Businger, A., *Helv. Chim. Acta* **24**, 339 (1941).

Rylander, P. N., and Himelstein, N., *Engelhard Ind. Tech. Bull.* **5**, 43 (1964).

Rylander, P. N., and Kreidl, J. F., U.S. Patent 3,193,584, July 6, 1965.

Rylander, P. N., and Steele, D. R., *Engelhard Ind. Tech. Bull.* **3**, 19 (1962).

Rylander, P. N., and Steele, D. R., *Engelhard Ind. Tech. Bull.* **3**, 125 (1963).

Rylander, P. N. and Steele, D. R., *Engelhard Ind. Tech. Bull.* **6**, 41 (1965a).

Rylander, P. N., and Steele, D. R., *Engelhard Ind. Tech. Bull.* **5**, 113 (1965b).

Schrecker, A. W., and Hartwell, J. L., *J. Am. Chem. Soc.* **75**, 5917 (1953).

Skita, A., and Rolfes, H., *Chem. Ber.* **53**, 1242 (1920).

Smith, H. A., and Stump, B. L., *J. Am. Chem. Soc.* **83**, 2739 (1961).

Smith, H. A., and Thompson, R. G., *Advan. Catalysis* **9**, 727 (1957).

Somerville, W. T., and Theimer, E. T., U.S. Patent 2,927,127, March 1, 1960.

Steele, D. R., Unpublished observations, Engelhard Ind., 1966.

Tomita, M., and Uyeo, S., *Nippon Kagako Zasshi* **63**, 1189 (1942).

Walker, G. N., *J. Am. Chem. Soc.* **80**, 645 (1958).

Walton, E., Wilson, A. N., Haven, A. C., Jr., Hoffman, C. H., Johnston, E. L., Newhall, W. F., Robinson, F. M., and Holly, F. W., *J. Am. Chem. Soc.* **78**, 4760 (1956).

Whitehead, C. W., Traverso, J. J., Marshall, F. J., and Morrison, D. E., *J. Org. Chem.* **26**, 2809 (1961).

Woodward, R. B., and Doering, W. E., *J. Am. Chem. Soc.* **67**, 860 (1945).

Zil'berman, E. N., *Khim. Prom.* p. 152 (1954).

20

Anilines

Hydrogenation of anilines usually affords a saturated amine as the major product

$$\text{C}_6\text{H}_5\text{–NH}_2 + 3\text{H}_2 \longrightarrow \text{C}_6\text{H}_{11}\text{–NH}_2$$
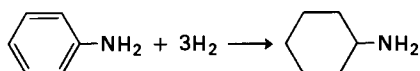
but several side-reactions may accompany and even dominate the reduction. These include hydrogenolysis,

$$\text{H}_2\text{N–C}_6\text{H}_4\text{–N}\overset{R}{\underset{R}{<}} + 4\text{H}_2 \longrightarrow \text{H}_2\text{N–C}_6\text{H}_{11} + \text{HN}\overset{R}{\underset{R}{<}}$$

reductive hydrolysis,

$$\text{C}_6\text{H}_5\text{–N}\overset{R}{\underset{R}{<}} + \text{H}_2\text{O} + 2\text{H}_2 \longrightarrow \text{C}_6\text{H}_{10}{=}\text{O} + \text{HN}\overset{R}{\underset{R}{<}}$$

and reductive coupling,

$$\text{C}_6\text{H}_5\text{–NH}_2 + 6\text{H}_2 \longrightarrow \text{C}_6\text{H}_{11}\text{–}\overset{H}{\text{N}}\text{–C}_6\text{H}_{11} + \text{NH}_3$$
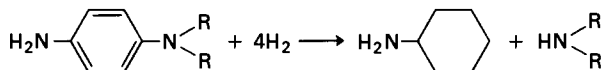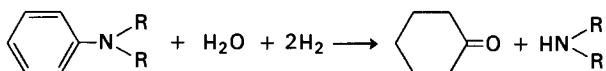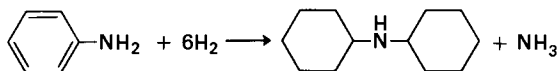
The products of reduction depend on a number of factors, among which are temperature, solvent, substrate, and catalyst.

Rates of hydrogenation of aniline over five platinum metals supported on carbon in various solvents have been measured (Rylander and Steele, 1962); the results are shown in Table I. Rhodium and ruthenium are particularly active, a factor accounting in part for the rapidly increasing interest in these catalysts.

TABLE I

HYDROGENATION OF ANILINE[a]

	Solvent					
Catalyst	None	Water	Acetic acid	Dimethyl-formamide		Ammonia (conc.)
Ir	<10	14	<10	<10	<10	—
Pd	43	31	167	<10	13	—
Pt	18	43	43	<10	10	—
Rh	195	258	139	16	148	249
Ru	98	174	112	50	100	78

[a] 300 mg 5% metal-on-carbon, 100°C, 1000 psig; 50 ml substrate without solvent, or 25 ml substrate and 25 ml solvent. Rate expressed in ml H_2/minute.

I. REDUCTION TO THE SATURATED AMINE

Platinum catalysts are no longer generally preferred, but have been used in reduction of anilines with success. For instance, dicyclohexylamine was obtained in excellent yield by reduction of diphenylamine hydrochloride over platinum oxide in ethanol at 50°C (Hiers and Adams, 1927). The reduction was not as successful if diphenylamine were used in ethanol containing hydrochloric acid. Best results were obtained when an ethanolic solution of diphenylamine hydrochloride was added to a suspension of platinum black, made by reducing platinum oxide in ethanol; the reduction was slower when platinum oxide was reduced in the presence of the substrate.

More recently, excellent results have been obtained in the reduction of aromatic amines over rhodium and ruthenium catalysts. Rhodium can be used under mild conditions, ruthenium apparently only under more vigorous conditions, as indicated by the following examples.

Hydrogenation of phenylenediamines over ruthenium dioxide in methylcyclohexane at 135–150°C and 1600 psig (Frunze et al., 1959) or in dioxane at 100°C and 1500–2500 psig (Kirby, 1952) affords diaminocyclohexanes in good yields. Over 5% rhodium-on-alumina in ethanol the reduction proceeds at 50 psig and 25°C (Shokal and Newey, 1957).

An interesting technique for obtaining pure cis-1,2-diaminocyclohexane has been patented (Smith, 1965). Urea and o-phenylenediamine are refluxed and then the product is reduced over ruthenium dioxide at 1500–3500 psig and 110–180°C. The resulting N,N'-cyclohexyleneurea is hydrolyzed with strong acid to liberate the pure cis isomer.
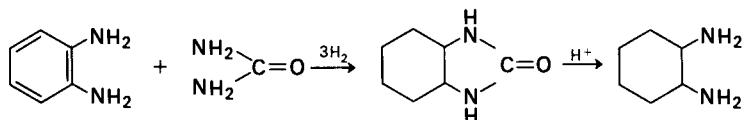
Ruthenium dioxide is an excellent catalyst for preparation of bis(4-amino-cyclohexyl)methane by hydrogenation of bis(4-aminophenyl)methane. Yields as high as 92% were obtained. The reductions were made in dioxane, or in anhydrous ammonia, or without solvent. The temperatures were generally 100–120°C and the pressures 2000–3000 psig. At 100–120°C only a small amount of the *trans,trans* isomer is formed; the product is mostly *cis,cis* and *cis,trans*. The amount of *trans,trans* isomer formed increases as the temperature is raised. Reduction over alkali-promoted cobaltic oxide catalyst gave mainly the *trans,trans* isomer. In contrast to the excellent results obtained with ruthenium, hydrogenation over platinum oxide in acetic acid at 50°C and 30–45 psig gave bis(4-aminocyclohexyl)methane in only 23% yield, accompanied by large amounts of polymeric material (Barkdoll *et al.*, 1953).
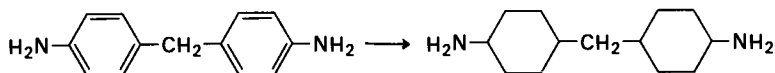
Freifelder and Stone (1962) reduced a series of 28 nuclear substituted anilines over ruthenium dioxide at 1050–1200 psig and 90–125°C in methanol or ethanol or without solvent. With a 2% catalyst loading the reduction was in general very rapid and the yields good, except where certain substituents made a hydrogenolysis or a coupling reaction prominent, as described below. Salts of phenylsulfamate may be reduced over rhodium or ruthenium catalysts to the cyclohexylamine acid salt in good yield. Ammonium phenylsulfamate gave ammonium cyclohexylsulfamate in 85% yield when reduced over ruthenium dioxide in water at 300 psig and 75–80°C. Ruthenium-on-alumina was also used at 80°C and 1200 psig (Freifelder, 1963). The same reduction can be achieved by 5% rhodium-on-alumina at 30 psig and room temperature (Freifelder *et al.*, 1961).
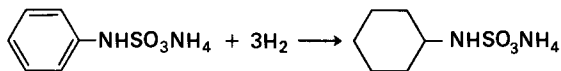
Cyclohexylamines may be obtained by reduction of the corresponding nitrobenzenes, the aniline occurring only as an unisolated intermediate. For instance, 4-nitroisopropylaniline was reduced over ruthenium dioxide at 80°C and 500–1500 psig. After sufficient hydrogen to reduce the nitro function had been absorbed, the temperature was raised to 100°C and the pressure to 2000–2500 psig to reduce the ring. *N*-Isopropyl-1,4-cyclo-hexanediamine was obtained, after distillation, in 43% yield (Behr *et al.*,

1946). Good yields of cyclohexylamines were obtained by reduction of either aromatic amines or aromatic nitro compounds over ruthenium dioxide in ethanol at 85–90°C and 2000 psig (Whitman, 1952).

II. SECONDARY AMINES

Hydrogenation of anilines may be accompanied by a coupling reaction to afford ultimately a saturated secondary amine, occasionally the major product of the reduction. The mechanism of secondary amine formation has been discussed by Greenfield (1964). In considering the reduction of aniline, he proposed the intermediate formation of enamines and imines, which then undergo addition of cyclohexylamine, followed by direct hydrogenolysis or by loss of ammonia and reduction. The process is similar to that proposed earlier to account for the formation of secondary amines in the reduction of nitriles (Von Braun *et al.*, 1923).

A. AMMONIA

As with nitriles, the coupling reaction in aniline hydrogenation can be decreased by addition of ammonia, but the technique is not without complication. Addition of anhydrous ammonia to the reduction mixture decreased the amount of dicyclohexylamine formed over ruthenium, but at the expense of a much lower rate of reduction. Rhodium was poisoned by ammonia. When aqueous ammonia was used with ruthenium the toxic properties of ammonia were eliminated (Maxted, 1951), and coupling was decreased without a decrease in rate. However, the yield of cyclohexylamine was not increased, as reductive hydrolysis leading to cyclohexanol became an important side-reaction.

B. SUBSTRATE

The extent of coupling depends on the substrate. Only unsubstituted and N-monoalkyl-substituted anilines can give coupled products, in accord with the suggestions of Greenfield (1964). Reduction of N-ethylaniline over colloidal platinum in aqueous acetic acid gave 40% of the coupled product, N-ethyldicyclohexylamine, while reduction of N,N-diethylaniline gave only N,N-diethylcyclohexylamine. Similar results were obtained with N-methyl- and N,N-dimethylaniline (Skita and Berendt, 1919). Formation of dicyclohexylamines may be prevented by acetylation prior to reduction but, at least in the case of platinum-catalyzed reductions, the rate of hydrogenation is greatly decreased (Skita and Rolfes, 1920).

Reduction of an acid salt instead of the free base may also prevent secondary amine formation. For instance, reduction of aniline in acetic acid over colloidal platinum gave 40% cyclohexylamine and 60% dicyclohexylamine. When the reduction was carried out in acetic acid–hydrochloric acid, cyclohexylamine was formed exclusively (Skita and Berendt, 1919).

The structural features determining the extent of coupling may be subtle indeed, as illustrated by the puzzling results obtained in reduction of eleven alkyl-substituted analines (Freifelder and Stone, 1962). Ten of these, including the isomeric toluidines and xylidenes, gave on reduction over ruthenium dioxide at 1050–1200 psig and 90–125°C the corresponding cyclohexylamine; no secondary amines were detected. In contrast, hydrogenation of 4-(2-pentyl)aniline resulted in only 11.5% of the cyclohexylamine; the major product was the secondary amine.
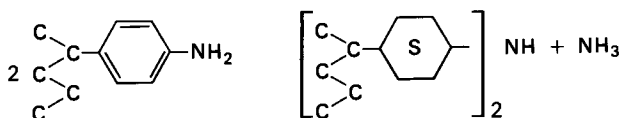
C. TECHNIQUES

A technique for preventing formation of dicyclohexylamines in catalytic reduction of anilines has been described by Duggan (1964). The hydrogenation is conducted at temperatures below the boiling point of the aniline and above that of the cyclohexylamine. By sweeping hydrogen through the solution the cyclohexylamine is removed from the reactor as fast as it is formed. The process is made continuous by adding substrate as the product is removed. A yield of 96.5% of cyclohexylamine was obtained in 24 hours at 155°C and 1 atm with 5% palladium-on-carbon at a 2% loading level. The actual rate of reduction under these conditions seems to be about 15–20 gm cyclohexylamine per gm catalyst per hour. A similar experiment, in which cyclohexylamine was continuously condensed and returned to the reactor, gave a 95% yield of high boiling by-products.

Another technique for inhibiting dicyclohexylamine formation has been described by Illich and Robinson (1960). The conversion of aniline to dicyclohexylamine was minimized by adding the coupled product to the feed. Reduction of aniline was carried out continuously at 200–260°C and 750 psig over a ruthenium-on-alumina catalyst, using a feed to which 15% of dicyclohexylamine had been added. The yield of cyclohexylamine was 82%. This technique is apparently applicable only when the reduction is carried out under vigorous conditions. In a few selected experiments made under mild conditions, the yield of cyclohexylamine was independent of the presence of dicyclohexylamine in the original substrate (Kilroy, 1964). Even under

somewhat more severe conditions, 145°C and 1000 psig, little inhibition of coupling was observed when this technique was employed (Greenfield, 1964).

D. TEMPERATURE

The extent of coupling depends on the temperature of reduction, increasing as the temperature is increased. Reduction of *m*-toluidine over platinum at 23–26°C gave 56% methylcyclohexylamine and 44% di(methylcyclo-hexyl)amine; at 55°C the yields were 21% and 79%, respectively. In reduction of *o*-toluidine, the coupled product increased from 16% to 58% when the temperature was raised from 23° to 55°C (Skita and Berendt, 1919).

E. SOLVENT

The solvent may also have considerable influence on the extent of coupling. Better yields of cyclohexylamine were obtained from hydrogenation in ethanol than in acetic acid over a rhodium-platinum catalyst. In ethanol, cyclohexylamine was obtained in 92% yield, unaccompanied by dicyclo-hexylamine. When only 1% of acetic acid was added to the ethanol the yield of cyclohexylamine dropped to 75%, and 12% of dicyclohexylamine was formed (Nishimura and Taguchi, 1963).

F. CATALYSTS

The ratio of primary to secondary amine formed in reduction of anilines depends on the catalyst. In a study on the reduction of aniline, Greenfield (1964) found that invariably more dicyclohexylamine was formed over 5% rhodium-on-carbon than over 5% ruthenium-on-carbon. A study of catalyst supports confirmed the greater tendency of rhodium to produce dicyclo-hexylamine. Aniline without solvent was reduced over 5% rhodium- and over 5% ruthenium-on-carbon, -barium sulfate, -strontium carbonate, -barium carbonate, and -kieselguhr at 1000 psig and 110–150°C, the tem-perature rising as the reduction proceeded (Rylander *et al.*, 1965). The yield of dicyclohexylamine in all rhodium reductions fell in the range 14.5–22%, and in all ruthenium reductions in the range <0.5–4.8%. The metal is of far greater influence on the product than the carrier.

Mixed rhodium–platinum catalysts, prepared by fusion of rhodium chloride and chloroplatinic acid with sodium nitrate, have been shown to be superior to platinum oxide alone for hydrogenation of aniline. The mixed catalysts were more active than platinum, as might be expected, and

the yield of cyclohexylamine was much greater and the yield of dicyclo-
hexylamine correspondingly less (Nishimura and Taguchi, 1963). Poor
yields of the corresponding saturated amine were obtained in reduction
of bis(4-aminophenyl)methane (Barkdoll et al., 1953) and benzidine over
platinum in acetic acid. Both reductions were accompanied by extensive
coupling and formation of polymeric material. In reduction of benzidine,
over 60% of the amine groups originally present were converted to ammonia
(Balas and Sevcenko, 1931).

In summary, secondary amine formation increases with the catalyst in
the order, ruthenium < rhodium < platinum. Ruthenium catalysts are
recommended when coupling is to be avoided.

III. HYDROGENOLYSIS

During reduction of anilines, hydrogenolysis of the carbon–nitrogen bond
may occur. This side-reaction seems to be important only with certain
activated molecules. For instance, hydrogenolysis was extensive in reduction
of 4-dimethylamino- and 4-diethylaminoaniline over ruthenium dioxide
at elevated temperature and pressure (Freifelder and Stone, 1962), and only
low yields of the corresponding diaminocyclohexanes were obtained. In
contrast, excellent yields of dimethylaminocyclohexane were obtained by
hydrogenation of N,N-dimethylaniline without solvent over ruthenium
dioxide at 100°C and 1000 psig (Steele, 1963). Hydrogenation of triphenyl-
amine over platinum oxide in ethanol-hydrochloric acid was accompanied
always by considerable hydrogenolysis, and the product was a mixture of
cyclohexane and di- and tricyclohexylamines (Hiers and Adams, 1927).

Anilines substituted by an oxygen function may undergo a loss of oxygen
during nuclear reduction. Hydrogenolysis might be expected to be par-
ticularly great when platinum catalysts are used. Reduction of m-amino-
phenol over platinum oxide afforded no 3-aminocyclohexanol, but instead
a mixture of cyclohexylamine, dicyclohexylamine, and 3-cyclohexyl-cyclo-
hexanol (Heckel and Adams, 1925). Considerable loss of the oxygen function
was observed in reduction of certain alkoxyanilines even over ruthenium,
a catalyst that has proved useful in reduction of phenols and alkoxybenzenes
when hydrogenolysis was to be avoided. The authors noted that the extent
of hydrogenolysis seemed inversely related to the size of the substituent
(Freifelder and Stone, 1962). Reduction of 2-methoxyaniline gave 2-methoxy-
cyclohexylamine in 42.5% yield, while 2-ethoxyaniline gave 2-ethoxycyclo-
hexylamine in 78.7% yield. Apparently no hydrogenolysis at all occurred
in reduction of 4-butoxyaniline. (Rhodium proved to be particularly useful
in hydrogenation of alkoxyanilines without extensive hydrogenolysis
(Freifelder, et al., 1965.)

Complete hydrogenolysis of the oxygen function during nuclear reduction of 4-aminoacetophenone has been reported; the only product was 4-ethylcyclohexylamine. However, Freifelder and Stone (1962), in a noteworthy reduction of this substrate over ruthenium dioxide at 60–105°C and elevated pressure, formed the saturated carbinol in 72% yield.
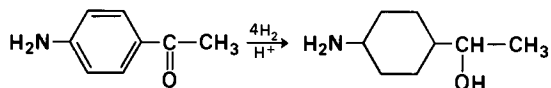
IV. HYDROLYSIS

Hydrogenation of aniline and its derivatives in aqueous media may be accompanied by products arising from reductive hydrolysis. The yield of these products depends on the substrate and catalyst and at times may be quite high. Hydrolytic cleavage is facilitated by substitution on the nitrogen atom. Reduction of aniline hydrochloride in water over palladium hydroxide-on-barium sulfate gave only about 10% cyclohexanone; reduction of N,N-dimethylaniline hydrochloride gave cyclohexanone in 56% yield. The reduction is believed to go through an imine-type intermediate (Kuhn and Haas, 1958).
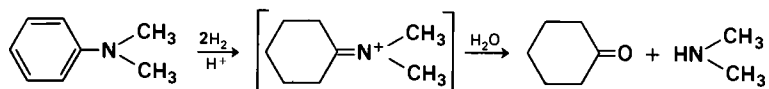
Quaternary anilinium compounds are not reduced. Trimethylphenylammonium chloride or iodide was unchanged in this system. p-Dimethylaminobenzoic acid gave 4-cyclohexanonecarboxylic acid in 20% yield, but the corresponding methyl betaine was not reduced. Reduction of diphenylamine hydrochloride in water gave cyclohexanone and aniline, each in 25% yield. Good yields of hydrolysis products are obtained from certain N-phenylamino acid derivatives.
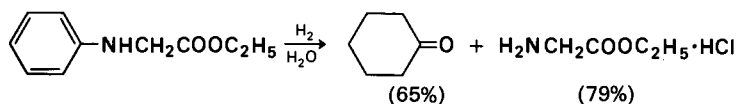
Palladium is probably the best of the platinum metals for hydrolytic reductions of this type. No ketone was formed from any substrate when platinum or nickel was used in place of palladium.

Under more vigorous conditions reductive hydrolysis will occur over other platinum metals. N,N-Dimethylaniline was reduced over 5% palladium-, platinum-, rhodium-, ruthenium-, and iridium-on-carbon in 25% aqueous sulfuric acid at 100°C and 1000 psig. The yields of cyclohexanol plus cyclo-

hexanone for palladium, rhodium, and platinum were 90%, 75%, and 13%, respectively (Steele, 1963). Ruthenium and iridium were poisoned in this system before reduction was complete. In another study on reduction of the isomeric toluidines in acidic media, ruthenium-on-carbon gave a greater yield of methylcyclohexanol than rhodium-on-carbon. Results from hydrogenations in dilute acetic acid are given in Table II. Hydrogenation of

TABLE II

HYDROGENATION OF TOLUIDINES: EFFECT OF METAL IN DILUTE ACETIC ACID[a]

Catalyst	Toluidine	Rate (ml H_2/min)	Percent trans-methylcyclo-hexylamine[b]	Percent methylcyclo-hexanol[c]
300 mg 5% Rh/C	ortho	250	14	10
600 mg 5% Ru/C	ortho	90	8	22
300 mg 5% Rh/C	meta	240	40	<1
600 mg 5% Ru/C	meta	60	15	20
300 mg 5% Rh/C	para	280	5	<3
600 mg 5% Ru/C	para	70	20	19

[a] Temperature: 100°C; pressure: 1000 psig; solvent: water containing 1.5 equivalents of acetic acid.
[b] Based on methylcyclohexylamine present.
[c] Based on C_7's present.

toluidenes was also carried out in dilute hydrochloric and in dilute sulfuric acid (Tables III and IV). The ruthenium catalysts were poisoned in the hydrochloric acid, but the reduction proceeded smoothly in sulfuric acid (Rylander and Steele, 1963).

TABLE III

HYDROGENATION OF TOLUIDINES IN DILUTE HCl[a]

Catalyst (300 mg)	Toluidine	Rate (ml H_2/min)	Percent trans-methylcyclo-hexylamine[b]	Percent methylcyclo-hexanol[c]
5% Rh/C	ortho	240	17	21
	meta	230	56	<5
	para	270	7	<5

[a] Temperature: 100°C; pressure: 1000 psig; solvent: water containing 1.5 equivalents of HCl.
[b] Based on methylcyclohexylamine present.
[c] Based on C_7's present.

<div align="center">

TABLE IV

HYDROGENATION OF TOLUIDINES IN DILUTE $H_2SO_4{}^a$

</div>

Catalyst (600 mg)	Toluidine	Rate (ml H_2/min)	Percent trans-methylcyclo-hexylamine[b]	Percent methylcyclo-hexanol[c]
5% Ru/C	ortho	213	5	11
	meta	115	14	<2
	para	90	17	6

^{a} Temperature: 100°C; pressure: 1000 psig; solvent: water containing 1.7 equivalents of H_2SO_4.

^{b} Based on methylcyclohexylamine present.

^{c} Based on C_7's present.

In summary, generalizing from a few particulars, palladium will cause the most hydrolytic cleavage of anilines in aqueous acidic media, platinum the least. This reaction can best be avoided entirely by use of nonaqueous solvents.

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REFERENCES

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Balas, F., and Sevcenko, P., *Collection Czech. Chem. Commun.* 3, 171 (1931).

Barkdoll, A. E., England, D. C., Gray, H. W., Kirk, W., Jr., and Whitman, G. M., *J. Am. Chem. Soc.* 75, 1156 (1953).

Behr, L. C., Kirby, J. E., MacDonald, R. N., and Todd, C. W., *J. Am. Chem. Soc.* 68, 1296 (1946).

Duggan, R. J., U.S. Patent 3,117,992, Jan. 14, 1964.

Freifelder, M., U.S. Patent 3,082,247, Mar. 19, 1963.

Freifelder, M., and Stone, G. R., *J. Org. Chem.* 27, 3568 (1962).

Freifelder, M., Meltsner, B., Illich, G. M., and Robinson, R. M., British Patent 882,952, Nov. 22, 1961.

Freifelder, M., Ng, Y. H., and Helgren, P. F., *J. Org. Chem.* 30, 2485 (1965).

Frunze, T. M., Korshak, V. V., and Romanova, Z. V., *Vysokomolekul. Soedin.* 1, 518 (1959).

Greenfield, H., *J. Org. Chem.* 29, 3082 (1964).

Heckel, H., and Adams, R., *J. Am. Chem. Soc.* 47, 1712 (1925).

Hiers, G. S., and Adams, R., *J. Am. Chem. Soc.,* 49, 1099 (1927).

Illich, G. M., Jr., and Robinson, R. M., British Patent 836,951, June 9, 1960.

Kilroy, M., Unpublished observations, Engelhard Ind., 1964.

Kirby, J. E., U.S. Patent 2,606,926, Aug. 12, 1952.

Kuhn, R., and Haas, H. J., *Ann. Chem.* 611, 57 (1958).

Maxted, E. B., *Advan. Catalysis* 3, 129 (1951).

Nishimura, S., and Taguchi, H., *Bull. Chem. Soc. Japan* 36 (7), 873 (1963).

Rylander, P. N., and Steele, D. R., *Engelhard Ind. Tech. Bull.* 3, 19 (1962).

Rylander, P. N., and Steele, D. R., *Engelhard Ind. Tech. Bull.* 4, 20 (1963).

Rylander, P. N., Kilroy, M., and Coven, V., *Engelhard Ind. Tech. Bull.* 6, 11 (1965).

Shokal, E. C., and Newey, H. A., U.S. Patent 2,817,644, Dec. 24, 1957.

Skita, A., and Berendt, W., *Chem. Ber.* **52B**, 1519 (1919).
Skita, A., and Rolfes, H., *Chem. Ber.* **53B**, 1242 (1920).
Smith, A. I., U.S. Patent 3,167,586, Jan. 26, 1965.
Steele, D. R., Unpublished observations, Engelhard Ind., 1963.
von Braun, J., Blessing, G., and Zobel, F., *Chem. Ber.*, **56B**, 1988 (1923).
Whitman, G. M., U.S. Patent 2,606,925, Aug. 12, 1952.

21

Furans

Hydrogenation of furans may yield products of ring addition—tetra-hydrofurans or in special cases dihydrofurans, or products of ring cleavage—alcohols, ketones, or hydrocarbons. Whether ring hydrogenation or ring hydrogenolysis occurs depends on the substrate, the catalyst, and the conditions of the reaction. The generality has been made that regardless of catalyst an increase in temperature will favor hydrogenolysis (Chouikine and Belsky, 1961), and at elevated temperature hydrogenolysis is sometimes the exclusive reaction. For instance, reduction of 2-methylfuran over platinum gave only pentanone-2 at 275°C (Chouikine and Belsky, 1957).

The hydrogenation of furans in the gas phase at elevated temperatures has been studied extensively. These vigorous conditions, through encouraging hydrogenolysis, gave a variety of products. Work in this area is mentioned only briefly in this report, as a discussion is beyond the scope of the present review, confined arbitrarily to liquid phase. A good paper on these gas phase reactions has been presented by Chouikine and Belsky (1961).

The furan nucleus is more easily reduced than that of benzene (Smith and Fuzek, 1949). Nonetheless, a variety of functional groups in substituted furans have been reduced without attack at the furan nucleus. (These examples are discussed under the section on the functional group undergoing reduction.)

I. HYDROGENATION OF THE FURAN NUCLEUS

The furan nucleus can be saturated by hydrogenation over each of the platinum metals. One study has divided the platinum metals into two types; platinum-, osmium-, iridium-, and ruthenium-on-carbon at 200–300°C tend to cause ring cleavage, while palladium- and rhodium-on-carbon tend to cause ring saturation over a wide temperature range (Chouikine and Belsky, 1961). Low temperature reductions of furans over platinum metal

catalysts are not numerous, but they too indicate that palladium and rhodium (and ruthenium) are useful for ring saturation, platinum for ring cleavage. Rhodium and palladium catalysts have each given good yields of saturated furans. Tetrahydrofuran was prepared in nearly quantitative yield by reduction of furan over palladous oxide at 100 psig. The reduction was carried out by adding the furan in small portions (20–30 gm) and additional catalyst with each portion. Reduction of 120 gm furan required 15–20 hours by this technique (Starr and Hixon, 1943). The reduction proceeded more rapidly in alcohol, but it was difficult to separate the product from the solvent. Platinum oxide was unsatisfactory for this reduction (Starr and Hixon, 1934). An essentially quantitative yield of tetrahydrofuran-2,3,4,5-d_4 was obtained by reduction of furan in deuterium at 800 psig over 5% rhodium-on-alumina (Bissell and Finger, 1959). Exchange reactions were evidently negligible. The authors give a discussion of the stereoisomers possible in this compound.
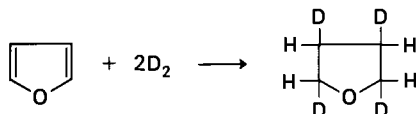
The reduction of the furoquinoline (I) over 5% palladium-on-carbon is interesting, in that it illustrates how sensitive the course of reduction may be to the reaction conditions. With a very dilute solution, 0.13 gm substrate in 100 ml 95% ethanol, and 0.02 gm 5% palladium-on-carbon at 50 psig and 54°C the dihydro compound (II) was obtained. When the concentration of substrate in solvent was raised above this amount an octahydro compound 2-isopropyl-4-oxo-2,3,4,5,6,7,8,9-octahydrofuro(3,2-c)quinoline, resulted. At temperatures less than 50°C no reduction occurred (Huffman and Browder, 1964).

(I)   (II)
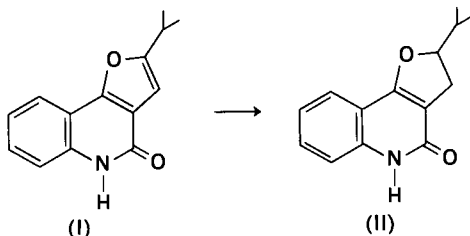
Platinum catalysts tend to cause hydrogenolysis of the furan ring, but in special circumstances fair yields of ring-saturated products may result.

(III)   (IV)
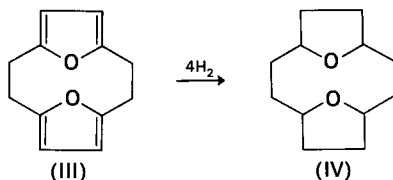
Hydrogenation of III over platinum oxide in acetic acid gave the saturated compound (IV) in 46% yield (Winberg *et al.*, 1960). In contrast, under the same conditions furan and 2,5-dimethylfuran were cleaved almost quantitatively to butanol and 2-hexanol, respectively (Smith and Fuzek, 1949).

Ruthenium has proved to be a useful catalyst for saturation of the furan ring at moderate temperatures. High pressures are evidently needed for satisfactory rates. For example, furfural and furylpropyl alcohol were reduced over ruthenium dioxide at 100°C and 1500 psig to the tetrahydro derivatives in excellent yields. Furylacrolein was reduced over ruthenium dioxide to a mixture containing 75.5% of the tetrahydropropanol and 16.7% of 1,6-dioxaspiro(4,4)nonane. Room temperature was sufficient to convert furfurylideneacetone and furylbutanone to the tetrahydrobutanols over a 5% ruthenium-on-carbon catalyst. Both ruthenium dioxide and ruthenium-on-carbon maintained activity for long periods of use (Ponomarev and Chegolya, 1962).

Ruthenium catalysts have proved useful in hydrogenation of amino furans and in reductive amination. A series of bis-amino tetrahydrofurans was prepared by reduction of the corresponding furan over 10% ruthenium-on-carbon in dioxane at 3000–6000 psig and 100–160°C. The yields were excellent since little hydrogenolysis occurred. It was not possible in this case to form the saturated amines in one step by reductive alkylation of the corresponding carbonyl, as ammonia prevented ring reduction (Webb and Borcherdt, 1951).
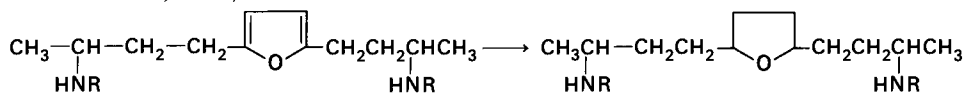
Reductive amination with simultaneous ring saturation was possible at 170°C over ruthenium dioxide. Hydrogenation of furfurylideneacetone (V) in the presence of ammonia gave the saturated amine (VI) in 61% yield. Reduction of 1-(α-furyl)-3-aminobutane to give VI occurred at room temperature and 1500 psig over 5% ruthenium-on-carbon (Ponomarev and Chegolya, 1962).
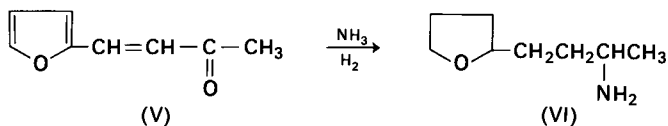
II. HYDROGENOLYSIS OF FURANS

Ring cleavage in hydrogenation of furans under mild conditions may occur very easily over platinum catalysts, especially in acidic media. Furfural

was reduced quantitatively over platinum oxide in ethanol to furfuryl alcohol and, if the reduction were allowed to continue, a mixture of tetra-hydrofurfuryl alcohol, pentanediol-1,2, pentanediol-1,5, and n-amyl alcohol was formed, the amounts of each decreasing in the order given. The importance of catalyst quality was stressed in this work. Platinum oxide made from very pure chloroplatinic acid was an ineffective catalyst, but the addition of small amounts of ferrous chloride converted it to an active catalyst (Kaufmann and Adams, 1923). In contrast to the above results, hydrogenation of furfuryl alcohol in acetic acid over platinum oxide gave almost quantitatively pentanediol-1,2 (Smith and Fuzek, 1949). Hydrogenation of furans in acetic acid over platinum oxide appears to favor strongly ring cleavage and, of a number of furans reduced, only dibenzofuran failed to undergo extensive hydrogenolysis. Dibenzofuran was completely reduced on absorption of six moles of hydrogen to dicyclohexene oxide. Apparently both rings were reduced before the molecule was desorbed from the catalyst, for when the reduction was interrupted after absorption of three moles of hydrogen only starting material and completely saturated product were found. Nearly quantitative yields of butanol and hexanol-2 were obtained in reduction of furan and 2,5-dimethylfuran over platinum oxide in acetic acid (Smith and Fuzek, 1949).
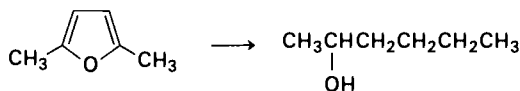
In unsymmetrical furans, the direction of ring opening depends on the substituents. With furoic acid, ring opening occurs at the carbon–oxygen bond nearest the carboxyl group, and γ-hydroxyvaleric acid (isolated as γ-valerolactone) is the major product. Less than 10% tetrahydrofuroic acid was formed. On the other hand, reduction of 2-methylfuran and furfuryl alcohol results in ring cleavage at the carbon–oxygen bond removed from the substituent. Furfuryl alcohol afforded 1,2-pentanediol almost quantitatively, and an 80–90% yield of sec-amyl alcohol resulted from reduction of 2-methylfuran; the remainder of the product was 2-methyltetrahydrofuran. It was shown that the tetrahydrofuran derivatives cannot be intermediates in the formation of these hydrogenolysis products (Smith and Fuzek, 1949). Hydrogenation of 2-phenylfuran over 5% palladium-on-carbon in acetic acid gave phenylbutanol by cleavage of the carbon–oxygen bond adjacent to the phenyl group:
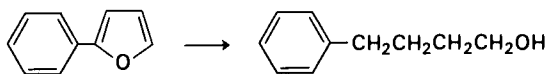
Similarly, reduction of 5-phenylfuran-2-carboxylic acid gave α-hydroxy-δ-phenylvaleric acid (Mitsui *et al.*, 1960):
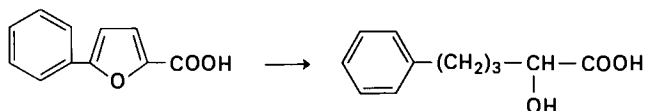
On reduction over platinum oxide in acetic acid, the complex ketonic furan (VII), called furopelargone A, absorbed three equivalents of hydrogen. The product contained a hydroxyl and a new ketonic function. The latter could have arisen only by hydrogenolysis of the furan ring. Further reduction of the ketone to an alcohol was prevented presumably by steric hindrance. Perhaps it is these same steric factors that prevented hydrogenolysis of the ring in the reverse sense. No reduction at all was observed over platinum- or palladium-on-carbon in ethanol, but this may have been because less metal (unstated) was used in the supported catalysts (Lukas *et al.*, 1964).

(VII)
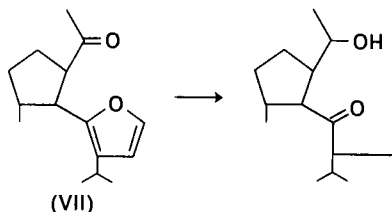
In aqueous media, hydrogenolysis may be accompanied by hydrolysis. 2-Methylfuran has been converted to 5-hydroxy-2-pentanone in 75% yield by hydrogenolysis over 5% palladium-on-carbon in acetone–dilute hydrochloric acid. Acetone or ethanol proved superior to dioxane, methanol, tetrahydrofuran, or formic acid in this reduction. A disadvantage of ethanol is that 2-ethoxytetrahydro-2-methylfuran is formed as a by-product. The *amount* of solvent was important. Best results were obtained with about equal weights of substrate and solvent (Londergan *et al.*, 1953).
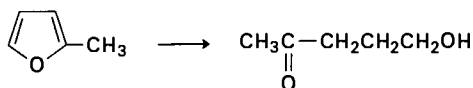
HYDROGENOLYSIS AT ELEVATED TEMPERATURE
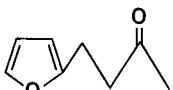
Hydrogenolysis over platinum metals of furans at elevated temperature has been the subject of a number of studies, a few of which are mentioned below.

Hydrogenation of 2-methyl-5-acetylfuran over palladium-, iridium-, osmium-, rhodium-, and ruthenium-on-carbon at 200–300°C gives mainly

2-methyl-5-ethylfuran and its hydrogenolysis products, 2- and 3-heptanones. Other products formed in the reduction were 3-methylcyclohexanone, 3-methylcyclohexanol, and *m*-cresol. Palladium-on-carbon gave the greatest amount of these secondary products; at 300°C it formed less of them than at 200°C, a fact explained by the authors as due to lower adsorption capability at the higher temperature. At 300°C palladium-on-carbon gave up to 40% *m*-cresol, 14% 2,6-dimethyltetrahydropyran, and a mixture of 2-methyl-5-ethylfuran and 2- and 3-heptanones (Shuikin *et al.*, 1962). Reduction over platinum-on-carbon at 275°C gave 3-methylcyclohexanone, 3-methylcyclohexanol, and *m*-cresol, possibly through cyclization of 2,6-heptanedione. At 270–300°C *m*-cresol was formed in 50% yield, but at 220°C was nearly absent (Shuikin and Bel'skii, 1959a). Hydrogenation of 2-methyl-5-acetylfuran over 10% platinum-on-asbestos at 200°C gave a 35% yield of 2,6-heptanedione (Shuikin and Vasilevskaya, 1964).

$$CH_3{-}\underset{O}{furan}{-}\underset{\underset{O}{\|}}{C}{-}CH_3 \longrightarrow CH_3\underset{\underset{O}{\|}}{C}{-}(CH_2)_3{-}\underset{\underset{O}{\|}}{C}CH_3$$
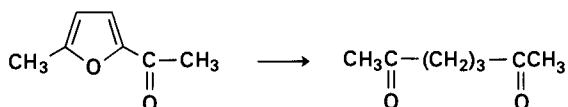
A study has been made on the effect of a carbonyl group, an α,β-unsaturated carbonyl, and a carbalkoxy group on the direction of hydrogenolysis of the furan ring. Hydrogenolysis was carried out in the vapor phase over 10% platinum-on-carbon at 250–60°C:

	2-heptanone	2-methyl-5 propyltetra hydrofuran	2,5-octane dione	2- and 4-octanones
[furan-CH=CH-C(=O) structure] →	40%	20%	26%	14%
[furan-CH2CH2-C(=O) structure] →	8%	22%	10%	60%

A similar reduction of ethyl β-furylacrylate gave 30% ethyl caproate and 65% ethyl γ-oxoenanthate; reduction of the corresponding propionate ester gave 7% ethyl caproate and 93% ethyl γ-oxoenanthate (Bel'skii *et al.*, 1962).

Sylvan (2-methylfuran) was converted almost completely to methyl propyl ketone over iridium, ruthenium (Shuikin *et al.*, 1959), or rhodium-on-carbon at 275–300°C (Shuikin and Bel'skii, 1959b). Osmium was less active

and gave only a 40% conversion. Hydrogenation of sylvan over 5% platinum-on-carbon at 250–260°C gave 100% methyl propyl ketone, but dihydrosylvan gave only 10% of the ketone and 90% tetrahydrosylvan. These results indicate that the dihydro compound is not an intermediate in the formation of the ketone (Shuikin et al., 1958). Hydrogenation of 2-methyl-5-ethylfuran over 15% platinum-on-carbon at 235°C gave 54% 3-heptanone and 36% 2-heptanone, indicating a slight preference for hydrogenolysis of the carbon–oxygen bond adjacent to the methyl group (Shuikin et al., 1957).

[References to the hydrogenation of furans over nonplatinum catalysts may be found in a review by Smith (1957).]

REFERENCES

Bel'skii, I. F., Shuikin, N. I., and Shostakovskii, V. M., Izv. Akad. Nauk SSSR Otd. Khim. Nauk p. 1821 (1962).

Bissell, E. R., and Finger, M., J. Org. Chem. 24, 1259 (1959).

Chouikine, N. I., and Belsky, I. F., Dokl. Akad. Nauk SSSR 115, 330 (1957).

Chouikine, N. I., and Belsky, I. F., Actes Congr. Intern. Catalyse, 2ᵉ, Paris, 1960 2, 2625 (1961).

Huffman, J. W., and Browder, L. E., J. Org. Chem. 29, 2598 (1964).

Kaufman, W. E., and Adams, R., J. Am. Chem. Soc. 45, 3029 (1923).

Londergan, T. E., Hause, N. L., and Schmitz, W. R., J. Am. Chem. Soc. 75, 4456 (1953).

Lukas, G., Ma, J. C. N., McCloskey, J. A., and Wolff, R. E., Tetrahedron 20, 1789 (1964).

Mitsui, S., Ishikawa, Y., and Takeuchi, Y., Nippon Kagaku Zasshi 81, 286 (1960).

Ponomarev, A. A., and Chegolya, A. S., Dokl. Akad. Nauk SSSR 145, 812 (1962).

Shuikin, N. I., and Bel'skii, I. F., Dokl. Akad. Nauk SSSR 127, 359 (1959a).

Shuikin, N. I., and Bel'skii, I. F., Zh Obsch., Khim. 29, 1093 (1959b).

Shuikin, N. I., and Vasilevskaya, G. K., Izv. Akad. Nauk SSSR Ser. Khim. 557 (1964).

Shuikin, N. I., Bel'skii, I. F., and Tyan, S.-K., Dokl. Akad. Nauk SSSR 116, 808 (1957).

Shuikin, N. I., Bel'skii, I. F., and Karakhanov, R. A., Dokl. Akad. Nauk SSSR 122, 625 (1958).

Shuikin, N. I., Bel'skii, I. F., Minachev, Kh. M., Zh. Obsch. Khim. 29, 2969 (1959).

Shuikin, N. I., Bel'skii, I. F., and Vasilevskaya, G. K., Zh. Obshch. Khim. 32, 2911 (1962).

Smith, H. A., In "Catalysis" (P. H. Emmett, ed.), Vol. 5, p. 175. Reinhold, New York, 1957.

Smith, H. A., and Fuzek, J. F., J. Am. Chem. Soc. 71, 415 (1949).

Starr, D., and Hixon, R. M., J. Am. Chem. Soc. 56, 1595 (1934).

Starr, D., and Hixon, R. M., In "Organic Syntheses," Vol. II, p. 566. Wiley, New York, 1943.

Webb, I. D., and Borcherdt, G. T., J. Am. Chem. Soc. 73, 752 (1951).

Winberg, H. E., Fawcett, F. S., Mochel, W. E., and Theobald, C. W., J. Am. Chem. Soc. 82, 1428 (1960).

22

Nitrogen Heterocyclic Compounds

I. PYRROLES

Pyrroles can be hydrogenated to pyrrolidines, the reduction proceeding sometimes stepwise through pyrroline intermediates. Acetic acid is frequently used as a solvent; the acidic medium probably helps to prevent deactivation of the catalyst by the basic nitrogen atom. In a comparison of solvents, acetic acid was preferred to methanol, ethanol, and dilute hydrochloric acid although all these solvents could be used; no reduction took place in ether, petroleum ether, or amyl alcohol (deJong and Wibaut, 1930). In another study, absolute alcohol containing a slight excess over an equivalent of hydrogen chloride was preferred to acetic acid (Craig and Hixon, 1930).

A. CATALYSTS

Platinum has been the most used of the platinum metals for reduction of pyrroles, but limited work suggests that rhodium may be a generally more useful catalyst. Palladium would seem to make a good catalyst for reduction of substituted pyrroles when saturation of the nucleus itself was to be avoided (Herz and Courtney, 1954). Palladium has been used, however, at 160°C for reduction of pyrrole and N-alkylpyrroles, which quickly poisoned platinum catalysts (Yur'ev and Shen'yan, 1934). N-Phenylpyrrole was reduced over platinum oxide in alcohol-hydrochloric acid to N-cyclohexylpyrrolidine. This reduction proceeded nonselectively; only a mixture of products was obtained when the hydrogenation was interrupted after two equivalents of hydrogen had been absorbed (Craig and Hixon, 1930). Platinum oxide in methanol was used for reduction of 2-(3,5-dimethyl-2-pyrrolyl)-1-pyrroline and ethyl 2,2'-pyrrolyl-1-pyrroline-5-carboxylate and afforded the corresponding 2-pyrrolylpyrrolidines in 95% and 71% yield, respectively (Atkinson et al., 1964).

Rhodium has proved to a useful catalyst for reduction of pyrroles (Skell and Bean, 1962). cis-2,5-Dimethylpyrrolidine was prepared by reduction of 2,5-dimethylpyrrole over 5% rhodium-on-alumina in acetic acid. The absorption of the first mole was rapid but that of the second was much slower, suggesting a stepwise reduction (Overberger et al., 1955). Ethyl pyrrolidylacetate was prepared conveniently by reduction of ethyl pyrrolyl-acetate over 5% rhodium-on-alumina in acetic acid (Adams et al., 1961). This method proved superior to the high pressure reduction over platinum oxide described earlier (Clemo and Melrose, 1942). Efforts to achieve reduction of pyrrolecarboxylic acid over platinum failed (McCay and Schmidt, 1926).
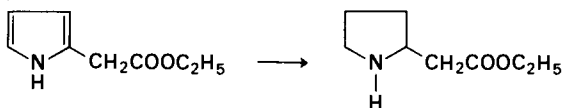
A synthesis of 1-amino-2,5-dimethylpyrrolidine involved hydrogenolysis of a carbobenzoxy group and selective hydrogenation of the pyrrole ring. The first step was carried out over 10% palladium-on-carbon in ethanol-acetic acid. The second step was carried out over 5% rhodium-on-carbon in acetic acid and, after absorption reached 112% of two equivalents, the reduction was stopped (Overberger et al., 1955).
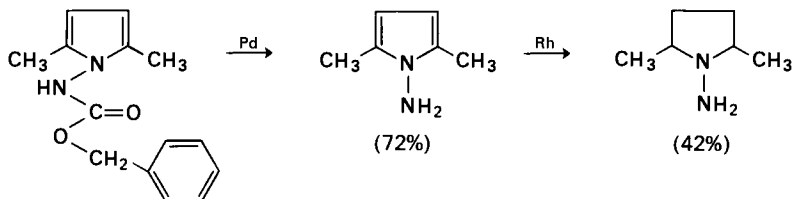
Rhodium was a useful catalyst in hydrogenation of 3H-pyrrolizine (I). The course and depth of hydrogenation were controlled conveniently by the solvent. Hydrogenation of 4.1 gm I in 50 ml anhydrous ether over 0.5 gm 5% rhodium afforded II in 81% yield. Reduction of either I or II in ethanol over 5% rhodium-on-carbon rapidly gave III in high yields (Schweizer and Light, 1966).
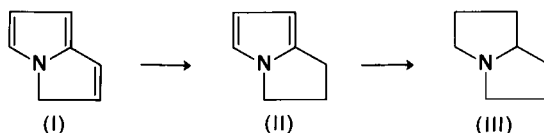
Catalyst Deactivation

A careful purification of the pyrrole may be necessary to assure a successful reduction (Andrews and McElvain, 1929). Some of the conflicting data on

the ease of reduction and effect of substitution has been attributed to the instability of pyrroles in air and to insufficient purification (Smith, 1957). Andrews and McElvain (1929) reduced pyrrole to pyrrolidine over platinum oxide in acetic acid solution, but the reduction could be made to go to completion only by frequent reactivation of the catalyst through shaking the reaction mixture with oxygen. Earlier workers had found also that frequent oxygen reactivation was necessary (Willstätter and Waldschmidt-Leitz, 1921), although a still earlier worker was careful to exclude any trace of oxygen to ensure a successful reduction (Hess, 1913).

Platinum oxide has been used to reduce a number of pyrroles, with varying degrees of success, a factor probably determined in large measure by the purity of the substrate. A mixture of α- and β-methylpyrroles could not be reduced over platinum oxide in acetic acid (Craig and Hixon, 1930), but 2-butylpyrrole was reduced to 2-butylpyrrolidine in 94% yield in the same type of system (Cantor and VanderWerf, 1958). Platinum oxide containing a small amount of ferric chloride in acetic acid-ethanol was used for hydrogenation of 2-pyrrolealdoxime, 2-pyrrolecarboxylic acid, and 2-pyrrole-methylamine (Putokhin, 1930). A special technique was necessary in these reductions to achieve the good yields reported. After about 10% of the theoretical hydrogen had been absorbed the reduction suddenly ceased. The addition of more catalyst alone at this stage did not induce further reduction. However, the addition of ethanol containing hydrochloric acid and ferric chloride together with more catalyst allowed the reduction to go to completion. If acetic acid or ethanol alone was used as the solvent, or if both were used but the hydrochloric acid was added at the beginning of the reduction, the results were very poor. Platinum oxide proved much better than palladium oxide in these reductions.

B. PYRROLINE INTERMEDIATES

Reductions of pyrroles may give intermediates that may undergo disproportionation to pyrroles and pyrrolidines (Wibaut and Proost, 1933). Partial hydrogenation of pyrrole over 5% rhodium-on-alumina without solvent gave, based on the hydrogen absorbed, a 31% yield of 1-pyrroline. Further hydrogenation gave pyrrolidine (Fuhlhage and VanderWerf, 1958):
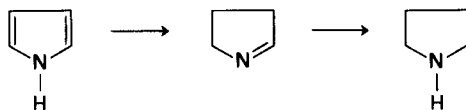
Yamamoto (1956) reduced several ethyl pyrrole-2-carboxylate derivatives over platinum oxide in ethanol containing a few drops of concentrated

hydrochloric acid. The products were the corresponding Δ^3-pyrroline and pyrrolidine. Hydrogenation of an acidified alcoholic solution of crypto-pyrrole (IV) over platinum oxide gave the 1-pyrroline (V) (Atkinson *et al.*, 1964), and not VI as previously reported. Hydrogenation of IV did not proceed in neutral or alkaline solution (Bullock, 1958).
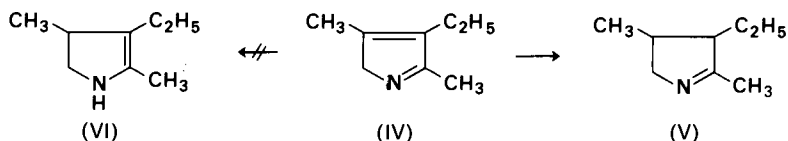
II. INDOLES

Indoles are reduced with relative difficulty, and the nucleus survives un-changed the hydrogenation of a number of substituent functions. When reduction of indole does occur, either or both rings may be hydrogenated and mixtures may result. Hydrogenation of indole over colloidal platinum in acetic acid afforded, after absorption of one mole of hydrogen, a mixture of unchanged indole, dihydroindole, and perhydroindole (Willstätter and Jaquet, 1918). 2,3-Dihydroindole is probably best obtained by hydrogena-tion over copper chromite (Adkins and Coonradt, 1941).

In acidic media the benzene ring of indole is reduced in preference to the pyrrole ring (Young and Snyder, 1961; Janot *et al.*, 1952; Karrer and Waser, 1949) and, in indole carrying pyridine (Schwarz and Schlittler, 1951) or isoquinoline substituents, the benzene ring is reduced in preference to either nitrogen ring (Boekelheide and Liu, 1952):
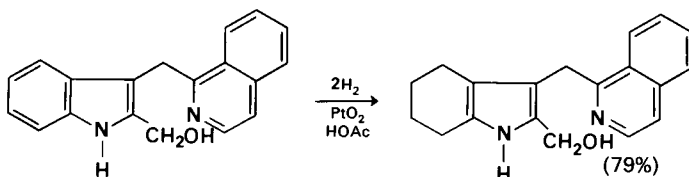
The solvent may have a decisive influence on the course of reduction. Virtually no reduction of VII occurred over platinum oxide in neutral or alkaline solution, but hydrogenation of 26 gm VII in 40 ml acetic acid and 120 ml ethanol over 0.65 gm platinum oxide afforded the skatylpiperidine (VIII) in 52% yield, the carbinol (IX) in 3.5% yield, and what appeared to be the symmetrical ether of X in 30% yield. The authors pointed out that the use of this slightly acid solvent provided for the first time a method

whereby a pyridine nucleus could be selectively reduced catalytically in the presence of the indole group (Bader and Oroshnik, 1957).

(VII)   (VIII)   (52%)

(IX)   (3.5%)   (X)   (30%)
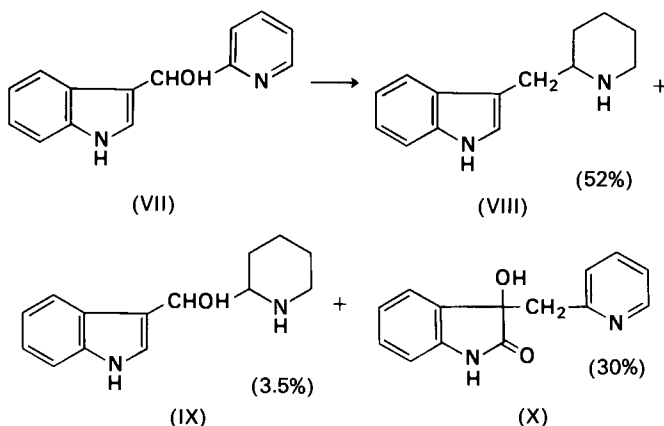
Hydrogenation of 3-indolyl-4′-pyridylcarbinol (XI) under the above conditions afforded only the hydrogenolysis product, 4-skatylpiperidine (XII), whereas reduction of the 3′-isoquinolyl derivative (XIII) gave the tetrahydro-isoquinolylcarbinol (XIV) in excellent yields (Bader and Oroshnik, 1959).

(XI)   (XII)

(XIII)   (XIV)
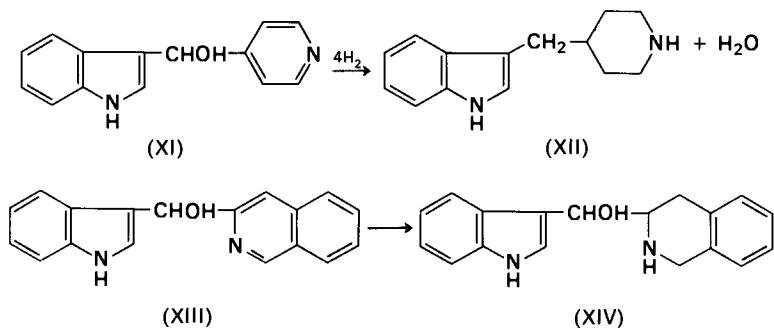
The facile hydrogenolyses leading to VIII and XII can be attributed to the presence of the indole nucleus and not the pyridine ring. A large number of compounds of the type,
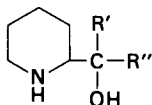
including some where R′ was aromatic, were prepared by reduction of the corresponding pyridine over platinum oxide without extensive hydrogenolysis (McCarty *et al.*, 1957).

III. PYRIDINES

Among the platinum metals, platinum has found the greatest popularity for hydrogenation of pyridines, but this probably stems more from early successes (Skita, 1915; Hamilton and Adams, 1928) than from an inherent and general superiority. Palladium (Lavagnino et al., 1960), rhodium (Freifelder et al., 1962), and ruthenium have been used relatively infrequently, although excellent results are at times obtained over these catalysts. Table I gives the rate of hydrogenation of pyridine over 5% palladium-, platinum-, rhodium-, and ruthenium-on-carbon in several solvents (Rylander and

TABLE I

HYDROGENATION OF PYRIDINE[a]

| Catalyst | Rate of hydrogenation (in ml H_2 absorbed/minute) in various solvents | | | | |
	None	Water	Acetic acid	Dimethyl-formamide	Methanol
Pd	117	136	398 (3)	35	85
Pt	<10	51	62 (3)	<10	22
Rh	894	400	372 (14)	248	813
Ru	44	231	158 (>1)	53	110

[a] 300 mg 5% metal-on-carbon, 100°C, 1000 psig; 50 ml substrate without solvent, or 25 ml substrate and 25 ml solvent. Figures in parentheses are rates obtained at room temperature and pressure (Coven, 1964).

Steele, 1962). The relative effectiveness of the catalysts in this test, as in all tests, is contingent on the particular conditions chosen. At room temperature and atmospheric pressure, rhodium appears relatively much more effective than under more vigorous conditions. Probably most pyridine systems could be reduced by rhodium under very mild conditions, but more effective use of this and other catalysts is made as the temperature and pressure are raised. For pyridine itself in acetic acid, palladium was moderately effective; with other pyridines, no reduction over palladium occurred at all unless the reaction temperature was 70–80°C (Walker, 1962). Under more vigorous conditions, ruthenium appeared to be a catalyst of considerable merit. Ruthenium is favored, for instance, for hydrogenation of pyridylalkanols; the reduction proceeds rapidly without side-reactions (Freifelder and Stone, 1961).

The catalyst support may have some influence on the reduction. Rhodium-on-carbon, although slower, gave a better yield than 5% rhodium-on-alumina in reduction in water of 2-(4-pyridyl)-2-methyl-1,3-dioxalane to the

corresponding piperidine. The yields from the carbon and alumina catalysts were 77% and 58%, respectively (Nielsen *et al.*, 1964).
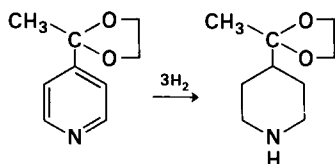
A. SOLVENT

A number of solvents—acidic, neutral, and basic—have been used successfully in pyridine hydrogenation. Acidic media are frequently used in reduction of pyridines to prevent inhibition of the catalyst by the basic nitrogen atom (Maxted and Walker, 1948), especially inhibition by the resulting more basic piperidine (Freifelder, 1963a). A variation, which accomplishes the same purpose, is reduction of a pyridine salt in neutral medium. Reduction of pyridine over platinum oxide proceeded poorly in most solvents due to poisoning of the catalyst, but pyridine hydrochloride was readily reduced; absolute alcohol was the best solvent and glacial acetic acid next best. Water inhibited the reduction markedly and no satisfactory results were obtained in 95% ethanol (Hamilton and Adams, 1928). The inhibiting effect of the basic piperidine nitrogen may be counteracted by internal neutralization; the pyridinecarboxylic acids, picolinic and isonicotinic acids, were readily reduced over platinum oxide in water (Freifelder, 1962).

Acid also changes the species actually undergoing hydrogenation from pyridine to pyridinium ions. The rate of hydrogenation of pyridine in acetic acid and sulfuric acid increases rapidly up to 0.5–1.5 mole ratios of pyridine to acid, reaches a maximum, and then decreases at mole ratios higher than 1.5. The authors suggested that the greater rate of hydrogenation of pyridinium ion may be due to a flat adsorption of the molecule on the catalyst surface, whereas the free base with an unshared pair of electrons may adsorb edgewise (Skomoroski and Schriesheim, 1961). The solvent played a major role in reduction of pyridotetrazole over 10% palladium-on-carbon. In acetic acid, a nearly quantitative yield of tetramethylenetetrazole was obtained and, in ammonium hydroxide, a moderate yield of 2-amino-pyridine without trace of tetramethylenetetrazole; in alcohol, a mixture of the two products was obtained (Boyer *et al.*, 1960).
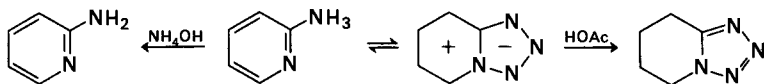
B. HYDROXYPYRIDINES

2-Hydroxypyridine and 4-hydroxypyridine are generally considered to be pyridones. Hydrogenation of 2-pyridone usually stops spontaneously at the 2-piperidone stage; the amide structure, as might be expected, resists further reduction. On the other hand, 4-pyridone is reduced to 4-hydroxypyridine inasmuch as no intermediate is particularly resistant to hydrogenation. Freifelder (1963a) reported that there is no record of reduction of 4-pyridones, which absorbed only two equivalents of hydrogen.

Walker and Weaver (1961) reduced 1 gm of the complex 2-pyridone (XV) to the corresponding 2-piperidone (XVI) in quantitative yield over 2 gm 10% palladium-on-carbon in 150 ml acetic acid at 75°C and 45 psig:

(XV)   (XVI)
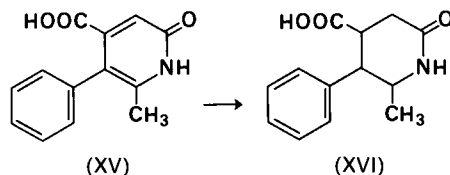
2-Pyridone has been reduced over palladium to 2-piperidone, but under the same conditions the 3- and 4-hydroxypyridines were not reduced (Cavallito and Haskell, 1944). At room temperature and pressure, 4-hydroxypyridine was resistant to hydrogenation over palladium, platinum, rhodium, and ruthenium in water and in acetic acid. In acetic anhydride solvent, fair rates of reduction were obtained under these mild conditions (Table II) (Rylander and Himelstein, 1963). A 75% yield, after distillation, of 4-hydroxypiperidine was obtained by hydrogenation of 4-pyridone over ruthenium dioxide in water. The reactions conditions were not stated but probably both elevated temperatures and pressures were used (Hall, 1958). Good yields of 4-piperidyl

TABLE II

REDUCTION OF 2- AND 4-PYRIDONE IN ACETIC ANHYDRIDE[a]

Catalyst	Amount of catalyst (mg)	Approximate ml H_2 absorbed/minute	
		2-Pyridone	4-Pyridone
PtO_2	500	50	26
5% Pd/C	1000	20	20
5% Pt/C	1000	9	5
5% Rh/C	1000	16	—
5% Ru/C	1000	0	0

[a] 1 gm pyridone, 50 ml acetic anhydride, room temperature and pressure.

ethers were obtained by reduction of 4-pyridyl ethers over ruthenium dioxide in methanol-water at 140°C and 2250 psig (Belgian Patent 626,774).

3-Hydroxypyridines have been reduced in excellent yield to the corresponding hydroxypiperidines. 5-Hydroxy-2-propylpyridine (1 gm), reduced over 250 mg platinum oxide in 50 ml acetic acid, afforded 5-hydroxy-2-propylpiperidine in 96% yield (Marion and Cockburn, 1949). Quantitative yields of 3-hydroxypiperidine were obtained by hydrogenation of 6.6 gm 3-hydroxypyridine hydrochloride in 75 ml absolute ethanol over 0.25 gm platinum oxide (Kao, 1948). Later workers were unable to repeat these results and under similar conditions obtained only 30–40% of 3-hydroxypiperidine and 70–60% piperidine (Biel et al., 1952). The facile hydrogenolysis was accounted for by an allylic type of intermediate. Perhaps the differences in results are a reflection of the pretreatment of and impurities in the platinum oxide, factors known to have marked effects on the degree of hydrogenolysis of allylic systems (Dart and Henbest, 1959). 3-Hydroxy-1-phenylpyridinium chloride also underwent extensive hydrogenolysis when reduced over platinum oxide in ethanol. There was isolated from the mixture a 34% yield of 1-phenylpiperidine and a 31% yield of 3-hydroxy-1-phenylpiperidine. Hydrogenolysis could be virtually eliminated, however, by reducing a solution of the substrate in alcohol or water that had been mixed with nearly one equivalent of sodium bicarbonate and then boiled with charcoal. Less than 3% of the hydrogenolysis product was found and 3-hydroxy-1-phenylpiperidine was obtained in 71–72% yield (Koelsch and Carney, 1950). 3-Hydroxypiperidine was obtained in 82% yield by hydrogenation of 3-hydroxypyridine over ruthenium dioxide in water (Hall, 1958).

Rhodium-on-carbon proved to be an excellent catalyst for reduction of 3-oxypyridyl betaines to the corresponding N-substituted-3-hydroxypiperidines. In compounds containing both the phenyl and pyridine rings, the latter was selectively reduced. There was no indication of reduction of the phenyl ring. But other functional groups are not necessarily invulnerable to reduction; phenacyl groups were reduced to the hydroxyl or to phenethyl, and the cyano group was reduced to the amine or bis-amine. A comparison of the actions of platinum dioxide and rhodium-on-carbon was made with a betaine (XVII). Both catalysts reduced the ring but platinum caused in addition extensive hydrogenolysis of the hydroxyl group (Shapiro et al., 1959).
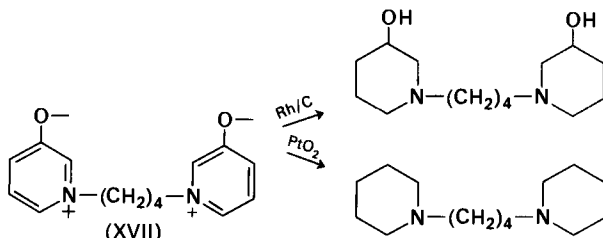
Hydrogenation of the 3-oxypyridyl betaine (XVIII) over 5% rhodium-on-carbon in methanol afforded selectively the 3-hydroxypiperidine (XIX) (Shapiro et al., 1962).

(XVIII)   (XIX)
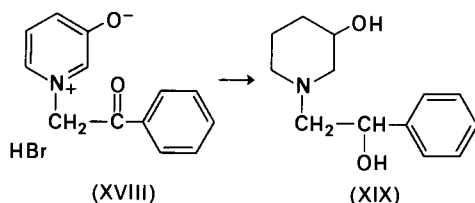
C. AMINOPYRIDINES

2-Aminopyridine and 4-aminopyridine, like the corresponding hydroxypyridines, can exist in tautomeric forms and behave similarly to the hydroxypyridines on hydrogenation. 3-Aminopyridine resembles aniline (Nienburg, 1937) on hydrogenation. Quantitative yields of 3-aminopiperidine dihydrochloride were obtained by hydrogenation of 3-aminopyridine over platinum oxide in hydrochloric acid solution. Ruthenium would probably also make a useful catalyst for this reduction, but apparently has not so far been used for the purpose. 4-Aminopyridine is reduced with considerable difficulty over platinum catalysts (Orthner, 1927) even at 80 atm (Yakhontov et al., 1958). Hydrogenation of N-(4-pyridyl)morpholine in water proceeded readily over ruthenium dioxide and elevated temperatures and pressures (Freifelder and Stone, 1961).

2-Aminopyridines, like 2-hydroxypyridines, tend to absorb only two moles of hydrogen, affording tetrahydro derivatives that resist further reduction. Hydrogenation of 2-aminopyridine in dilute hydrochloric acid over platinum afforded only 2-iminopiperidine; platinum oxide was more active than platinum black in this reduction. The acidic solution stabilized the substrate against deamination; when the reduction was carried out in neutral solution four moles of hydrogen were absorbed, resulting in piperidine and ammonia (Graves, 1924). Reduction of 2-aminopyridine over platinum oxide in acetic anhydride–acetic acid solution is said to absorb three equivalents of hydrogen to afford the saturated derivative, N,N'-diacetyl-2-aminopiperidine in 80% yield (Kirsanov and Ivashchenko, 1936). Hydrogenation of 2-benzylaminopyridine over palladium oxide in acetic acid afforded 2-benzylamino-3,4,5,6-tetrahydropyridine (Birkofer, 1942). Hydrogenation of 2-diethylaminopyridine and 2-dimethylaminopyridine led only to the corresponding 3,4,5,6-tetrahydropyridines over either rhodium-on-alumina or platinum oxide. Neither of these compounds is capable of tautomerizing. A solution of 22.5 gm 2-diethylaminopyridine, 100 ml acetic acid, and 9.0 gm 5%

rhodium-on-alumina absorbed only two equivalents despite the high catalyst loading and acidic conditions (Freifelder *et al.*, 1964).

R = CH$_3$, C$_2$H$_5$
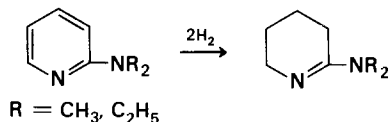
Catalytic hydrogenation of 7-azaindole, which may be viewed as a substituted 2-aminopyridine, also gave only a partially reduced product:

R = H, CH$_3$
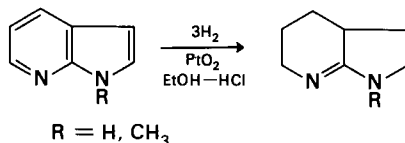
However, four moles of hydrogen were rapidly absorbed on hydrogenation of XX, followed by slower absorption of a fifth mole. The product (XXI) resulted from hydrogenolysis of the pyrrolidine ring (Robison *et al.*, 1957).
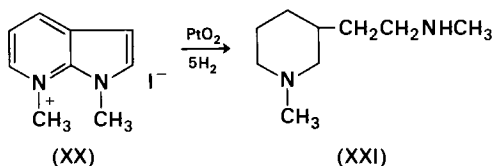
Carbon–nitrogen bond cleavage occurred also in reduction of XXII over 5% rhodium-on-carbon in ethanol affording XXIII in quantitative yield, but the hydrochloride salt of XXII was stabilized against deamination and XXIV was obtained in 98% yield (Shapiro *et al.*, 1961). It is noteworthy that the benzyl hydroxyl resisted hydrogenolysis in these reductions over rhodium.

R = —CH$_2$CHC$_6$H$_5$
              |
              OH

(XXIV)
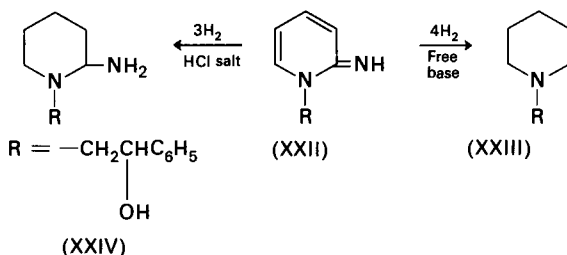
D. PYRIDINECARBOXYLIC ACIDS

Hydrogenation of pyridinecarboxylic acids proceeds readily over platinum metal catalysts. Hydrogenation of nicotinic acids (Sorm, 1948), but not

picolinic or isonicotinic acids, is apt to be accompanied by extensive de-
carboxylation. If the hydrogenation of nicotinic acids is carried out in the
presence of one equivalent of base, as sodium bicarbonate, sodium hydroxide
(Raasch, 1962), or ammonia, decarboxylation may be prevented. Hydrogena-
tion of 0.5 mole of nicotinic acid in 300 ml water containing 0.5 mole of
sodium bicarbonate over 1.22 gm ruthenium dioxide at 95°C and 1500 psig
afforded sodium nipecotate in 85% yield (Freifelder and Stone, 1961).
Reduction in the presence of ammonia allows isolation of nipecotic acid by
merely concentrating the solution after removal of the catalyst. Reduction
of 6.15 gm nicotinic acid in 50 ml water containing 6 ml concentrated aqueous
ammonia over 2.4 gm 5% rhodium-on-alumina at room temperature and
2 atm was complete in 4 hours or less. The catalyst was removed and the
solution evaporated to dryness in the presence of benzene to ensure complete
removal of water. The yield of sharply melting nipecotic acid was 88.5%
(Freifelder, 1963b). Reduction of nicotinic acid over rhodium or platinum
oxide in water without ammonia is accompanied by extensive decarboxyla-
tion (Freifelder, 1962).

Excellent yields of piperidine-2-carboxylic acid were obtained by
hydrogenation of 12.3 gm picolinic acid in 150 ml water over 0.25 gm
platinum oxide at 2.4 atm (Freifelder, 1962). The same product has been
obtained in almost quantitative yield by reduction of picolinic acid over
palladium-on-carbon at 60°C and 3 atm. Palladium, however, is much less
active in these reductions than platinum or rhodium (Freifelder, 1963a).
Quantitative yields of nipecotic acid hydrochloride have been obtained by
hydrogenation of 50 gm nicotinic acid hydrochloride in 125 ml water over
1 gm platinum oxide. After 10 hours the catalyst was reactivated by shaking
the reaction mixture with air; the total reaction time was 24 hours. Oxygen
is said to be much more efficient than air in the reactivation step (McElvain
and Adams, 1923). N-Methylisonipecotic acid hydrochloride was prepared
in 71% overall yield from isonicotinic acid in two steps without isolation of
the intermediate. Isonicotinic acid was first reduced over platinum oxide in
acetic acid–water at 1000 psig. The catalyst was then filtered, formaldehyde
and 9% palladium-on-carbon were added, and the hydrogenation was
continued (Clarke et al., 1949).

E. DIPYRIDYLS

Dipyridyls are easily reduced to dipiperidyls over platinum oxide in water
or alcohol containing an excess of hydrochloric acid. Under these conditions
no intermediate product is found; half-hydrogenation yields only a mixture
of dipyridyl and dipiperidyl (Smith, 1928). Platinum in neutral solution is
easily poisoned in these reductions, and rhodium under mild conditions

has been reported to be unsatisfactory in either neutral or acetic acid conditions (Freifelder, 1963a). Reduction of 2,2'-dipyridyl over palladium in neutral solution at elevated temperatures and pressures gave a fair yield of intermediate piperidylpyridine, but rhodium under the same conditions reduced much of the starting material directly to the dipiperidyl (Table III) (Rylander and Steele, 1965).

TABLE III

HYDROGENATION OF 2,2'-DIPYRIDYL[a]

Catalyst (300 mg)	Dipyridyl (% by wt)	Piperidylpyridine (% by wt)	Dipiperidyl (% by wt)	H_2 (moles)
5% Pd/C	44	50	6	1.90
5% Rh/C	51	10	39	2.64

[a] Reductions carried out at 100–120°C, 1000 psig, with 2.0 gm dipyridyl in 25 ml cyclohexane.

F. PARTIAL RING REDUCTION

Most pyridine compound are reduced to the corresponding piperidines but certain substituents arrest the hydrogenation at the tetrahydropyridine stage. Partial reduction usually occurs with 2-amino- and 2-hydroxy-pyridines, affording tetrahydro derivatives. An unexpected partial reduction occurred in hydrogenation of 3-acetylpyridine (XXV) over palladium. Hydrogenation of 45 gm XXV in 250 ml absolute ethanol over 5 gm 5% palladium-on-carbon was allowed to continue until absorption ceased. Distillation afforded the tetrahydro derivative (XXVI) in 70% yield. The author believed that XXVI was formed through 1,4-addition followed by saturation of the isolated double bond; XXVI resisted further reduction over palladium in either neutral or acid solution (Freifelder, 1964).

(XXV)   (XXVI)
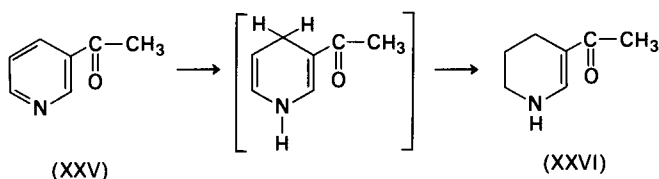
N-Alkyl-β-acylpyridinium salts undergo similar partial hydrogenation and afford vinylogous amides. A reduction of this type was a key step in the synthesis of indole alkaloids. Hydrogenation of 2.14 gm XXVII over 0.40 gm 10% palladium-on-carbon in 70 ml ethanol containing 4.3 ml triethylamine ceased in 5.5 hours and afforded 1.60 gm crude XXVIII. Some of the

hexahydropiperidine derivative was also isolated from the reaction mixture (Wenkert and Wickberg, 1965).

(XXVII)   (XXVIII)
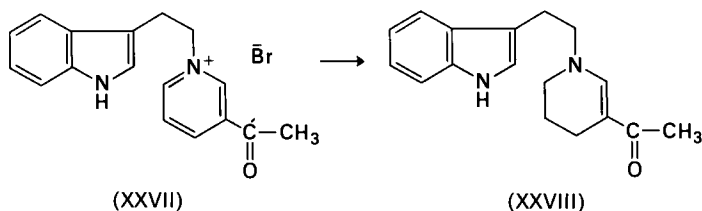
Partial saturation of quaternary pyridinium salts is not uncommon. Partial reduction is favored by limited time of hydrogenation, by limited catalyst, and by catalyst deactivators. By limiting hydrogen absorption, methyl N-methyl-tetrahydroisonicotinate was formed by reduction of the methiodide of methyl isonicotinate over platinum oxide in methanol; extended reaction times produced the hexahydro derivative (Supniewski and Serafinowna, 1936). At lower catalyst levels, 0.3 gm platinum per 21 gm methyl isonicotinate methiodide, the reduction ceased spontaneously at the tetrahydro stage (Lyle and Lyle, 1954). Much improved yields of the tetrahydro compound were obtained when a reused platinum oxide was employed (Lyle et al., 1955).

G. REDUCTIVE HYDROLYSIS

Partial hydrogenation of N-alkylpyridinium salts in the presence of one equivalent of alkali provides a convenient synthesis of ω-alkylamino-valeraldehydes, a class of compounds obtained otherwise only with difficulty. A sharp decline in rate is usually observed after absorption of two moles of hydrogen, and the hydrogenation should be interrupted at this point. Raney nickel and palladium hydroxide-on-barium sulfate are satisfactory catalysts. The reduction is best carried out at 0–5°C to prevent destruction of the product by the alkaline solution and to prevent overhydrogenation to the alkylpiperidine (Schöpf et al., 1957).
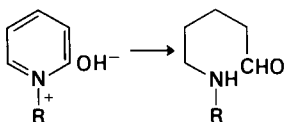
H. QUATERNARY COMPOUNDS

Quaternary pyridinium salts are readily reduced over platinum metal catalysts, offering a convenient way of obtaining N-substituted piperidines

(Hamilton and Adams, 1928; Grigor'eva *et al.*, 1957; Hayes *et al.*, 1956). The reduction may pass through a tetrahydropyridine stage, and in certain cases good yields of *N*-alkyltetrahydro derivatives may be obtained if the reduction is interrupted or if a less active catalyst is used (Lyle and Lyle, 1954; Lyle *et al.*, 1955). Partial reduction seems to be facilitated by electron-withdrawing substituents in the 3-position (Lyle and Mallett, 1966), if suitable conjugation with the substituent is possible; Jones (1966) has pointed out that 3-sulfonamide and 3-trifluoromethyl pyridines do not yield partially hydrogenated derivatives.

Reduction of *N*-alkylpyridinium halides proceeds most easily when the alkyl group is not branched. Reduction of lower *N*-alkylpyridinium halide esters afforded *N*-alkylpiperidine esters in good yields, but reduction of *N*-isopropyl or *N*-isobutyl methyl isonicotinate halides gave only low yields of impure esters. In contrast, quaternization of methyl isonicotinate with isopropyl *p*-toluenesulfonate followed by catalytic reduction of the crude quaternary salt afforded methyl *N*-isopropylisonipecotate in 90% yield (Sperber *et al.*, 1959). Quaternary pyridinium salts may be reduced more easily than hydrohalide salts, which in turn may be reduced more easily than the free pyridine base. This sequence offers some possibility of controlling selectivity by carrying out reductions with the pyridine nucleus in appropriate form. An example is the hydrogenation of 2-phenacylpyridine (XXIX). Reduction of XXIX in neutral solution over platinum oxide afforded the alcohol (XXX) (Scheuing and Winterhalder, 1929), reduction in acetic acid afforded the ring-saturated alcohol (XXXI), and reduction of the methobromide (XXXII) (Howton and Golding, 1950) or metho-*p*-toluenesulfonate

(XXXII) X⁻ = Br⁻
(XXXIII) X⁻ = CH₃—⟨ ⟩—SO₃⁻
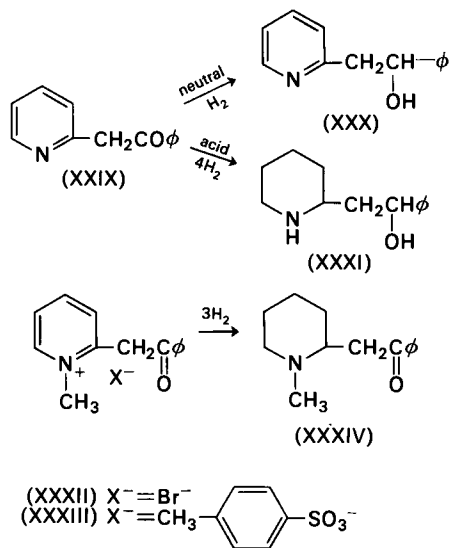
(XXXIII) afforded 1-methyl-2-phenacylpiperidine (XXXIV) (Lukes *et al.*, 1956). [Selective reduction of pyridines containing ketonic functions has been discussed at greater length by Freifelder (1963a).]

Platinum oxide proved much superior to 5% palladium-on-carbon for reduction of 2- or 4-stilbazole methiodides in methanol:
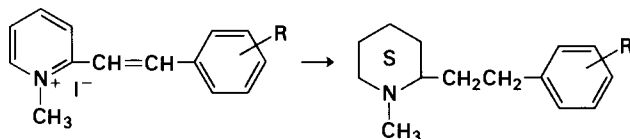
There was no evidence of poisoning of platinum oxide during these reductions, but palladium-on-carbon was completely and irreversibly poisoned by small amounts of iodide ion. The author felt that, since the original intense orange-red color remained until hydrogenation was virtually complete, the ring and olefin must have been reduced in a single residence of substrate on the catalyst (Phillips, 1950).

IV. QUINOLINES AND ISOQUINOLINES

Quinolines are reduced preferentially in the hetero ring and if the reduction is prolonged both rings may be saturated. The reduction seems unusually sensitive to poisons; quinolines obtained from different sources gave quite different rates of reduction even after various efforts to purify the substrate (Steele, 1964). As with pyridines, reduction of quinoline proceeds less readily as the free base than as an acid salt or quaternary compound. Complete reduction of quinoline in acetic acid over platinum gives predominantly the *trans* isomer, whereas reduction of the hydrochloride salt in ethanol (Overhoff and Wibaut, 1931) or in acetic acid containing excess hydrogen chloride gives mixtures of *cis* and *trans* isomers (Hückel and Stepf, 1927).

Isoquinolines are also reduced preferentially in the nitrogen ring (Walters *et al.*, 1961; Elliott and Leflore, 1963). Further reduction to the decahydro derivative is much more difficult than with quinoline and a number of failures have been reported. In some cases success has been achieved only when equal weights of substrate and platinum oxide were used in the presence of sulfuric acid (Witkop, 1948). Freifelder (1963a) attributed the difficulty in reducing the benzene ring of isoquinoline to poisoning of the catalyst by the basic nitrogen atom. He pointed out that 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, in which the poisoning effect of the nitrogen is neutralized by the carboxyl group, could be reduced to the decahydro derivative over 5% rhodium-on-carbon at 50°C, whereas the corresponding ethyl ester could not (Rapala *et al.*, 1957). The ester was converted instead to 3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline. Some preliminary evidence (unspecified)

indicated that tetrahydroisoquinolines substituted in the benzene ring were reduced to the decahydro derivatives with the substituents retained (Rapala et al., 1957). Good yields of decahydroisoquinoline could be obtained by hydrogenation of isoquinoline over ruthenium at 90°C and 1050 psig (Freifelder, 1963a). Reduction of tetrahydroisoquinolines to the decahydro compounds is facilitated greatly if the poisoning effect of the nitrogen atom is diminished through acetylation (Woodward and Doering, 1945).

Carbonyl compounds condense with isoquinolines under hydrogenation conditions to give 4-substituted tetrahydroisoquinolines. Reduction of iso-quinoline or quaternary salts over platinum oxide in the presence of aromatic aldehydes or cyclohexanone gives unstable 1,2-dihydro derivatives, which condense with the carbonyl compound and are stabilized by further reduction (Grewe et al., 1964).
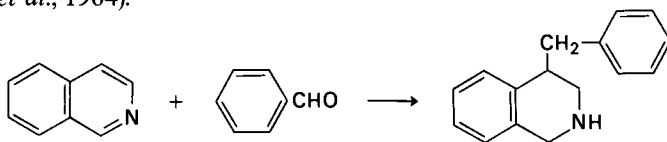
SUBSTITUTED QUINOLINES

The rate of reduction of aromatic rings decreases as the number and bulk of alkyl ring substituents increase (Gilman and Cohn, 1957). It might therefore be expected that alkyl substituents in the nitrogen ring of quinoline would increase the relative ease of saturation of the benzene ring, and vice versa. This proves to be the case. Substituents in the benzene ring strongly favor formation of 1,2,3,4-tetrahydro derivatives, whereas substitution in the pyridine ring increases the amount of 5,6,7,8-tetrahydro derivative (von Braun et al., 1922, 1923, 1924). However, 2-phenyl substituents afford first the 1,2,3,4-tetrahydro derivative (Oldham and Johns, 1939) and, if the reduc-tion is continued, the 2-cyclohexyl-1,2,3,4-tetrahydro compound and finally the decahydro derivative.

Hydroxy Substituents

Cavallito and Haskell (1944) examined the hydrogenation of a number of quinolinols and their esters in dioxane or ethanol over a palladium sponge catalyst; platinum oxide or Raney nickel was ineffective under the conditions used with palladium. Reduction of 2-quinolinol and 1-isoquinolinol afforded dihydroquinolones in close analogy to the conversion of 2-pyridinol to α-piperidone:
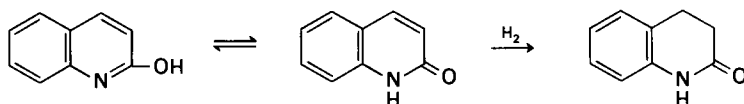
4-Quinolinol could not be reduced, but the 3-, 5-, 6-, 7-, and 8-quinolinols each afforded the corresponding 1,2,3,4-tetrahydroquinolinols. Reduction of 8-quinolinyl esters to the 1,2,3,4-tetrahydro derivatives was accompanied by migration of the acyl group to the nitrogen.
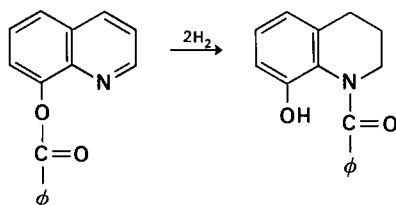
5-Hydroxy-2-ethylisoquinolinium bromide was smoothly reduced to the 1,2,3,4-tetrahydro derivative over platinum oxide, but attempts to produce the decahydro derivative led to an unusual product. Hydrogenation of the isoquinolinium bromide over platinum oxide in glacial acetic acid containing a small amount of sulfuric acid (Witkop, 1948) gave, as the only product isolated, bis(2-ethyldecahydroisoquinoline) ether. The ether was formed during the reduction, as 5-hydroxy-2-ethyldecahydroisoquinoline was recovered unchanged when subjected to the reaction conditions (Mathison, 1965).
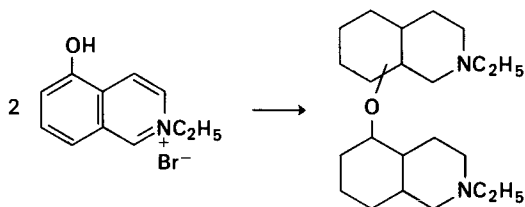
Hydrogenation of 3-hydroxyquinoline-8-carboxylic acid led to the 5,6,7,8-tetrahydro derivative (Ochiai et al., 1960), a most surprising reaction considering that 3-hydroxyquinoline and 8-carboxyquinoline are each converted to the 1,2,3,4-tetrahydro derivative (Campbell et al., 1946).

V. IMIDAZOLES

The imidazole ring is difficult to reduce (Hofmann, 1953). Reduction of a series of benzyl- and phenylethylimidazoles over platinum oxide, in acetic, dilute hydrochloric, or sulfuric acid, saturated the phenyl ring and left the imidazole ring unchanged (Schubert et al., 1962). Hydrogenation of 2-alkyl- and 1,2-dialkylbenzimidazoles over platinum oxide in acetic acid resulted only in saturation of the benzene nucleus (Hartmann and Panizzon, 1938).

Reduction over 5% palladium-on-carbon of 4-(benzylmethylaminomethyl)-imidazole in methanol containing hydrogen chloride gave 4-(methylamino-methyl(imidazole in 75% yield. The authors noted that only the benzyl group was split off and not the 4-methyleneimidazole group, which can be considered a benzyl-type radical. The imidazole nucleus also resisted hydrogenation in several other similar reductions (Turner et al., 1949).

A facile hydrogenation of the imidazole ring may be achieved by carrying out the reduction in acetic anhydride. Platinum oxide (1.0 gm) was reduced with hydrogen in acetic anhydride (150 ml) until absorption ceased. To this pretreated catalyst, 2.04 gm imidazole was added and hydrogenation continued until absorption ceased in about 7 hours. The acetic anhydride solution was decomposed with ice water and evaporated. Recrystallization of the remaining oil afforded diacetylimidazolidine in 80% yield. Diacetyl-benzimidazoline was similarly prepared from benzimidazole in 86% yield. Hydrogen absorption in these reductions was greater than theoretical because of partial reduction of the solvent (Bauer, 1961).

IMIDAZOLONES

Imidazolones are reduced smoothly over platinum oxide but the reduction is slow. Hydrogenation of 11.5 gm 2-imidazolone-4(5)-propionic acid in 280 ml acetic acid over 1.5 gm platinum oxide required 16 hours for theoretical absorption. 2-Imidazolidone-4(5)-propionic acid was isolated in 85% yield (Beiler et al., 1960).

The imidazolone nucleus is reduced with relative difficulty, as shown by the sequential reduction of 4-methyl-5-benzoylimidazolone-2 (XXXV). The

deoxy compound (XXXVI) could be obtained in 50% yield by limited reduction over platinum oxide in acetic acid, and in 87% yield over palladium-on-carbon. If the hydrogenation over platinum oxide were allowed to consume five equivalents of hydrogen, the phenyl ring was also saturated (XXXVII); absorption of six equivalents afforded the imidazolidone (XXXVIII). This last reduction was carried out at atmospheric pressure and also at 20 atm (Duschinsky and Dolan, 1945).

Preferential reduction of the ketonic function is not limited to benzyl ketones. Compound XXXIX underwent hydrogenolysis to give XL in 70% yield over platinum oxide in acetic acid and in 47% yield over 2.5% palladium-on-carbon at 140°C and 90 atm. Further reduction of XL over platinum oxide gave imidazolidone-2 (XLI) in 60% yield (Duschinsky and Dolan, 1945).
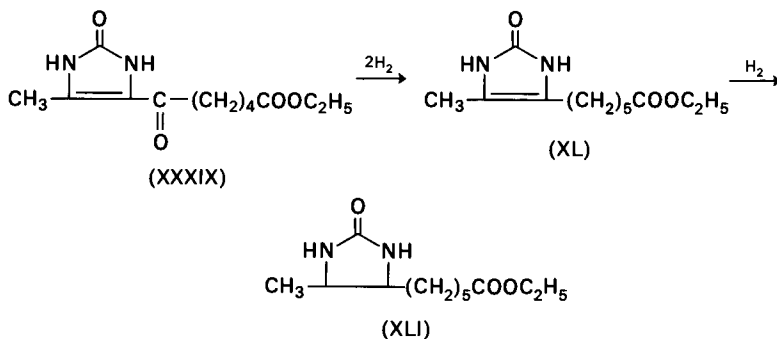
VI. PYRIDAZINES

Simple pyridazines are relatively few and have been little studied. No references to the hydrogenation of this group over platinum metals were found. The ring appears to be more resistant to hydrogenation than the isomeric pyrimidines or pyrazines. Certain pyridazines are in fact best prepared by hydrogenation. For instance, the pyridazine nucleus remained unchanged when 4-methyl-3,6-dichloropyridazine was dehydrohalogenated over 5% palladium-on-carbon in ethanolic ammonium hydroxide to give 4-methylpyridazine in 91% yield (Mizzoni and Spoerri, 1954). High yields of 3-aminopyridazine were similarly obtained (Steck et al., 1954).

VII. PYRAZINES

Pyrazines are readily hydrogenated under mild conditions to either fully or partially reduced derivatives. 2-Alkylpiperazines are prepared easily by

reduction of 2-alkylpyrazines over palladium-on-carbon in 95% ethanol at 45–60 psig (Behun and Levine, 1961). Similarly, pyrazine-2-carboxylic acid was reduced over 10% palladium-on-carbon in dilute potassium hydroxide at 50°C to piperazine-2-carboxylic acid in 94% yield (Felder *et al.*, 1960).
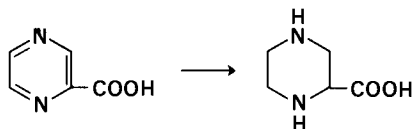
Pyrazinecarboxylic esters with several substituents were only partially reduced. Reduction of 2,3-dicarbomethoxypyrazine over 10% palladium-on-carbon gave the tetrahydro derivative (Mager and Berends, 1959), whereas the tetrasubstituted pyrazine (XLII) gave the dihydropyrazine (XLIII) on reduction over 5% platinum-on-alumina (Mager and Berends, 1957):

$$R = -COOC_2H_5$$
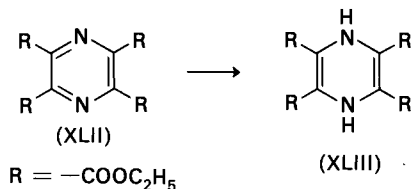
Pyrazines have also been reduced under vigorous conditions. Supported rhodium or palladium has been used to convert pyrazine or 2,5-dialkyl-pyrazines to the corresponding piperazines at 125–225°C and 450–600 psig pressure (Scigliano, 1958).

Benzopyrazines (quinoxalines) are readily reduced with the heterocyclic ring being preferentially saturated. Good yields of 1,2,3,4-tetrahydro-quinoxalines were obtained by hydrogenation of quinoxaline in benzene over platinum oxide. The reduction ceased spontaneously. Prior to introduction of platinum oxide, the reaction mixture was shaken with moist Raney nickel to remove poisons and then filtered (Cavagnol and Wiselogle, 1947).
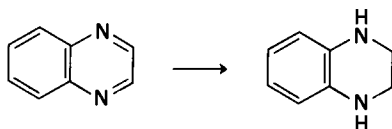
Palladium-on-carbon can also be used satisfactorily for saturation of the nitrogen ring. Hydrogenation and dehydrohalogenation of 2-chloro-3-methylquinoxaline in acetic acid containing sodium acetate over 5% palladium-on-carbon at 60°C and 30 psig gave 2-methyl-1,2,3,4-tetrahydro-quinoxaline in 65% yield. The same compound was obtained by reduction of 2-methylquinoxaline (Munk and Schultz, 1952).

VIII. PYRIMIDINES

Catalytic hydrogenation of pyrimidines is complex and, depending on the substrate and conditions, yields fully and partially reduced derivatives (Henze and Winthrop, 1957) as well as those obtained by hydrogenolysis of substituents and by hydrolysis. Platinum, palladium, and rhodium catalysts have been used in these reductions with varying success (Aft and Christensen, 1962). It might be anticipated from the aromatic character of pyrimidine and from its similarity to pyridine that rhodium and ruthenium would prove to be useful catalysts in reduction of pyrimidines. Rhodium, in fact, although not extensively employed, has already proved useful (Cohn and Doherty, 1956).

A. AMINOPYRIMIDINES

Evans (1964) has examined the hydrogenation of aminopyrimidines over 10% palladium-on-carbon. In acidic media, 2-aminopyrimidine and its 4,6-dimethyl and acyl derivatives absorbed two moles of hydrogen to give the corresponding 2-amino-1,4,5,6-tetrahydropyrimidines:
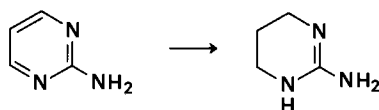
4-Aminopyrimidine was reduced slowly and gave unstable products. Reduction of 5-aminopyrimidine, its 2,4-dichloro derivative, and 5-nitro-2,4-dichloropyrimidine all gave the same product, 1,4,5,6-tetrahydro-5,5-dihydroxypyrimidine hydrochloride. The *gem*-diol arises through hydrolysis and hydration of an intermediate enamine.
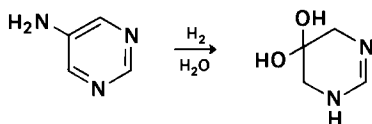
Reduction of cytosine (XLIV) over platinum oxide in dilute hydrochloric acid resulted in hydrogenolysis of the exocyclic amino nitrogen and formation of XLV (Wempen *et al.*, 1965). The method provided an elegant one for determination of isotopic distribution of labeled nitrogen.
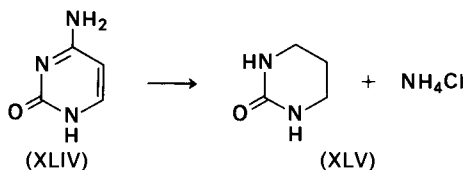
B. HYDROXYPYRIMIDINE

Hydroxypyrimidines exist primarily in the pyrimidone structure (Brown *et al.*, 1955; Short and Thompson, 1952) and catalytic hydrogenation of these compounds usually ceases with the carbonyl function remaining, even under vigorous conditions (Batt *et al.*, 1954). *N,N'*-Trimethyleneurea (XLVII) was obtained by hydrogenation of 2-hydroxypyrimidine (XLVI) over 5% rhodium-on-alumina in water. However, 4-hydroxypyrimidine was resistant to hydrogenation under the same conditions (Fox and Van Praag, 1960).

(XLVI)   (XLVII)
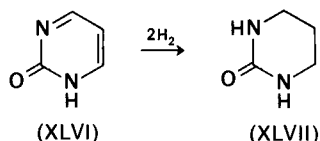
Rhodium proved useful in achieving a saturation of the carbon–carbon double bond in 5-hydroxymethyluracil without hydrogenolysis of the allylic hydroxyl. Catalytic hydrogenation over platinum oxide in 50% acetic acid gave the hydrogenolysis product, thymine in 95% yield. Over 5% rhodium-on-alumina in water the saturated hydroxymethyl compound was obtained in about 50% yield. The yield of the latter depends on the pH and decreases as the system becomes more acid; in 50% acetic acid very little was formed. Thymine is easily reduced further, but the saturated hydroxymethyl compound is not (Cline *et al.*, 1959) (see page 435).

Hydrogenation of pyrimidones in aqueous media may be accompanied by hydrolysis. Hydrogenation of 4-pyrimidone-6-carboxylic acid (XLVIII) over 5% rhodium-on-alumina in water was complex and led to three major components: formiminoaspartic acid (XLIX), methyleneasparagine (L), and asparagine (LI). No hydrogenation occurred in dimethylformamide, *N*-ethylmorpholine, or dimethyl sulfoxide (Kny and Witkop, 1959).

(XLVIII)   (XLIX)   (L)   (LI)
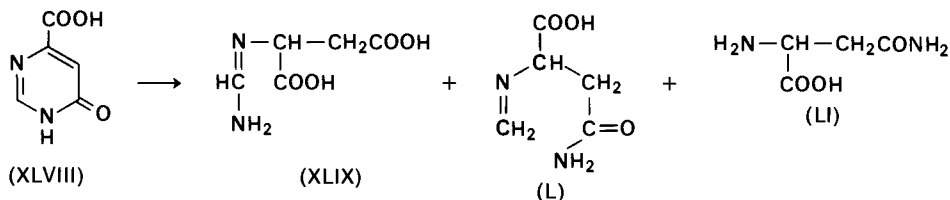
REFERENCES

Adams, R., Miyano, S., and Nair, M. D., *J. Am. Chem. Soc.* **83**, 3323 (1961).
Adkins, H., and Coonradt, H. L., *J. Am. Chem. Soc.* **63**, 1563 (1941).
Aft, H., and Christensen, B. E., *J. Org. Chem.* **27**, 2170 (1962).
Andrews, L. H., and McElvain, S. M., *J. Am. Chem. Soc.* **51**, 887 (1929).

Atkinson, J. H., Grigg, R., and Johnson, A. W., *J. Chem. Soc.* p. 893 (1964).

Bader, H., and Oroshnik, W., *J. Am. Chem. Soc.* **79**, 5686 (1957).

Bader, H., and Oroshnik, W., *J. Am. Chem. Soc.* **81**, 163 (1959).

Batt, R. D., Martin, J. K., Ploeser, J. McT., and Murray, J., *J. Am. Chem. Soc.* **76**, 3663 (1954).

Bauer, H., *J. Org. Chem.* **26**, 1649 (1961).

Behun, J. D., and Levine, R., *J. Org. Chem.* **26**, 3379 (1961).

Beiler, T. W., Plato, C. H., and Shepard, K. E., *J. Org. Chem.* **25**, 2236 (1960).

Biel, J. H., Friedman, H. L., Leiser, H. A., and Sprengeler, E. P., *J. Am. Chem. Soc.* **74**, 1485 (1952).

Birkofer, L., *Chem. Ber.* **75**, 429 (1942).

Boekelheide, V., and Liu, C-T., *J. Am. Chem. Soc.* **74**, 4920 (1952).

Boyer, J. H., Chang, M. S., and Reinisch, R. F., *J. Org. Chem.* **25**, 286 (1960).

Brown, D. J., Hoerger, E., and Mason, S. F., *J. Chem. Soc.* p. 211 (1955).

Bullock, E., *Can. J. Chem.* **36**, 1686 (1958).

Campbell, K. N., Kerwin, J. F., LaForge, R. A., and Campbell, B. K., *J. Am. Chem. Soc.* **68**, 1844 (1946).

Cantor, P. A., and VanderWerf, C. A., *J. Am. Chem. Soc.* **80**, 970 (1958).

Cavagnol, J. C., and Wiselogle, F. Y., *J. Am. Chem. Soc.* **69**, 795 (1947).

Cavallito, C. J., and Haskell, T. H., *J. Am. Chem. Soc.* **66**, 1166 (1944).

Clarke, R. L., Mooradian, A., Lucas, P., and Slauson, T. J., *J. Am. Chem. Soc.* **71**, 2821 (1949).

Clemo, G. R., and Melrose, T. A., *J. Chem. Soc.* p. 424 (1942).

Cline, R. E., Fink, R. M., and Fink, K., *J. Am. Chem. Soc.* **81**, 2521 (1959).

Cohn, W. E., and Doherty, D. G., *J. Am. Chem. Soc.* **78**, 2863 (1956).

Coven, V., Unpublished observations, Engelhard Ind., 1964.

Craig, L. C., and Hixon, R. M., *J. Am. Chem. Soc.* **52**, 804 (1930).

Dart, M. C., and Henbest, H. B., *Nature* **183**, 817 (1959).

deJong, M., and Wibaut, J. P., *Rec. Trav. Chim.* **49**, 237 (1930).

Duschinsky, R., and Dolan, L. A., *J. Am. Chem. Soc.* **67**, 2079 (1945).

Elliott, I. W., and Leflore, J. O., *J. Org. Chem.* **28**, 3181 (1963).

Evans, R. F., *J. Chem. Soc.* p. 2450 (1964).

Felder, E., Maffei, S., Pietra, S., and Pitré, D., *Helv. Chem. Acta* **43**, 888 (1960).

Fox, J. J., and Van Praag, D., *J. Am. Chem. Soc.* **82**, 486 (1960).

Freifelder, M., *J. Org. Chem.* **27**, 4046 (1962).

Freifelder, M., *Advan. Catalysis* **14**, 203 (1963a).

Freifelder, M., *J. Org. Chem.* **28**, 1135 (1963b).

Freifelder, M., *J. Org. Chem.* **29**, 2895 (1964).

Freifelder, M., and Stone, G. R., *J. Org. Chem.* **26**, 3805 (1961).

Freifelder, M., Robinson, R. M., and Stone, G. R., *J. Org. Chem.* **27**, 284 (1962).

Freifelder, M., Mattoon, R. W., and Ng, Y. H., *J. Org. Chem.* **29**, 3730 (1964).

Fulhage, D. W., and VanderWerf, C. A., *J. Am. Chem. Soc.* **80**, 6249 (1958).

Gilman, G., and Cohn, G., *Advan. Catalysis* **9**, 733 (1957).

Graves, T. B., *J. Am. Chem. Soc.* **46**, 1460 (1924).

Grewe, R., Krueger, W., and Vangermain, E., *Chem. Ber.* **97**(1), 119 (1964).

Grigor'eva, N. E., Oganes'yan, A. B., and Mysh, I. A., *Zh. Obshch. Khim.* **27**, 1565 (1957).

Hall, H. K., Jr., *J. Am. Chem. Soc.* **80**, 6412 (1958).

Hamilton, T. S., and Adams, R., *J. Am. Chem. Soc.* **50**, 2260 (1928).

Hartmann, M., and Panizzon, L., *Helv. Chim. Acta* **21**, 1692 (1938).

Hayes, F. N., King, L. C., and Peterson, D. E., *J. Am. Chem. Soc.* **78**, 2527 (1956).

Henze, H. R., and Winthrop, S. O., *J. Am. Chem. Soc.* **79**, 2230 (1957).

Herz, W., and Courtney, C. F., *J. Am. Chem. Soc.* **76**, 576 (1954).

Hess, K., *Chem. Ber.* **46**, 3113 (1913).

Hofmann, K., "Imidazole and Its Derivatives" Wiley (Interscience), New York, 1953.

Howton, D. R., and Golding, D. R. V., *J. Org. Chem.* **15**, 1 (1950).

Hückel, W., and Stepf, F., *Ann. Chem.* **453**, 163 (1927).

Janot, M., Keufer, J., and LeMen, J., *Bull. Soc. Chim. France* 230 (1952).

Jones, W. H., Personal communication, 1966.

Kao, C-H., *J. Chem. Eng. China* **15**, 80 (1948).

Karrer, P., and Waser, P., *Helv. Chim. Acta* **32**, 409 (1949).

Kirsanov, A. V., and Ivashchenko, Ya. N., *Bull. Soc. Chim.* **3**[5], 2279 (1936).

Kny, H., and Witkop, B., *J. Am. Chem. Soc.* **81**, 6245 (1959).

Koelsch, C. F., and Carney, J. J., *J. Am. Chem. Soc.* **72**, 2285 (1950).

Lavagino, E. R., Chauvette, R. R., Cannon, W. N., and Kornfeld, E. C., *J. Am. Chem. Soc.* **82**, 2609 (1960).

Lukes, R., Kovar, J., and Blaha, K., *Collection Czech. Chem. Commun.* **21** 1475 (1956).

Lyle, R. E., and Lyle, G. G., *J. Am. Chem. Soc.* **76**, 3536 (1954).

Lyle, R. E., and Mallett, S. E., *Conf. Catalytic Hydrogenation Analogous Pressure Reactions, New York, June, 1966.*

Lyle, R. E., Perlowski, E. F., Troscianiec, H. J., and Lyle, G. G., *J. Org. Chem.* **20**, 1761 (1955).

McCarty, F. J., Tilford, C. H., and Van Campen, M. G., Jr., *J. Am. Chem. Soc.* **79**, 472 (1957).

McCay, C. M., and Schmidt, C. L. A., *J. Am. Chem. Soc.* **48**, 1933 (1926).

McElvain, S. M., and Adams, R., *J. Am. Chem. Soc.* **45**, 2738 (1923).

Mager, H. I. X., and Berends, W., *Rec. Trav. Chim.* **76**, 28 (1957).

Mager, H. I. X., and Berends, W., *Rec. Trav. Chim.* **78**, 109 (1959).

Marion, L., and Cockburn, W. F., *J. Am. Chem. Soc.* **71**, 3402 (1949).

Mathison, I. W., *J. Org. Chem.* **30**, 3558 (1965).

Maxted, E. B., and Walker, A. G., *J. Chem. Soc.* p. 1093 (1948).

Mizzoni, R. H., and Spoerri, P. E., *J. Am. Chem. Soc.* **76**, 2201 (1954).

Munk, M., and Schultz, H. P., *J. Am. Chem. Soc.* **74**, 3433 (1952).

Nielsen, A. T., Moore, D. W., Mazur, J. H., and Berry, K. H., *J. Org. Chem.* **29**, 2898 (1964).

Nienburg, H., *Chem. Ber.* **70B**, 635 (1937).

Ochiai, E., Kaneko, C., Shimada, I., Murata, Y., Kosuge, T., Miyashita, S., and Kawasaki, C., *Chem. Pharm. Bull. (Tokyo)* **8**, 126 (1960).

Oldham, W., and Johns, I. B., *J. Am. Chem. Soc.* **61**, 3289 (1939).

Orthner, L., *Ann. Chem.* **456**, 225 (1927).

Overberger, C. G., Palmer, L. C., Marks, B. S., and Byrd, N. R., *J. Am. Chem. Soc.* **77**, 4100 (1955).

Overhoff, J., and Wibaut, J. P., *Rec. Trav. Chim.* **50**, 957 (1931).

Phillips, A. P., *J. Am. Chem. Soc.* **72**, 1850 (1950).

Putokhin, N. J., *Zh. Russ. Fiz.-Kkim. Obshchestva* **62**, 2216 (1930).

Raasch, M. S., *J. Org. Chem.* **27**, 1406 (1962).

Rapala, R. T., Lavagnino, E. R., Shepard, E. R., and Farkas, E., *J. Am. Chem. Soc.* **79**, 3770 (1957).

Robison, M. M., Butler, F. P., and Robison, B. L., *J. Am. Chem. Soc.* **79**, 2573 (1957).

Rylander, P. N., and Himelstein, N., Unpublished observations, Engelhard Ind., 1963.

Rylander, P. N., and Steele, D. R., *Engelhard Ind. Tech. Bull.* **3**, 19 (1962).

Rylander, P. N., and Steele, D. R., *Engelhard Ind. Tech. Bull.* **5**, 113 (1965).

Scheuing, G., and Winterhalder, L., *Ann. Chem.* **473**, 126 (1929).

Schöpf, C., Herbert, G., Rausch, R., and Schröder, G., *Angew. Chem.* **69**, 391 (1957).

Schubert, H., Berg, W. V., and Andrae, H., *Wiss. Z. Martin-Luther Univ. Halle-Wittenberg, Math.-Nat. Reihe* **11**(5), 603 (1962).

Schwarz, H., and Schlitter, E., *Helv. Chim. Acta* **34**, 629 (1951).

Schweizer, E. E., and Light, K. K., *J. Org. Chem.* **31**, 870 (1966).

Scigliano, J. J., U.S. Patent 2,843,589, July 15, 1958.

Shapiro, S. L., Weinberg, K., Bazga, T., and Freedman, L., *J. Am. Chem. Soc.* **81**, 5146 (1959).

Shapiro, S. L., Soloway, H., and Freedman, L., *J. Org. Chem.* **26**, 818 (1961).

Shapiro, S. L., Freedman, L., and Weinberg, K., U.S. Patent 3,056,797, Oct. 2, 1962.

Short, L. N., and Thompson, H. W., *J. Chem. Soc.* p. 168 (1952).

Skell, P. S., and Bean, G. P., *J. Am. Chem. Soc.* **84**, 4655 (1962).

Skita, A., *Chem. Ber.* **48**, 1486 (1915).

Skomoroski, R. M., and Schriesheim, A., *J. Phys. Chem.* **65**, 1340 (1961).

Smith, C. R., *J. Am. Chem. Soc.* **50**, 1936 (1928).

Smith, H. A., *Catalysis* **5**, 175 (1957).

Sorm, F., *Collection Czech. Chem. Commun.* **13**, 57 (1948).

Sperber, N., Sherlock, M., Papa, D., and Kender, D., *J. Am. Chem. Soc.* **81**, 704 (1959).

Steck, E. A., Brundage, R. P., and Fletcher, L. T., *J. Am. Chem. Soc.* **76**, 3225 (1954).

Steele, D. R., Unpublished observations, Engelhard Ind., 1964.

Supniewski, J. V., and Serafinowna, M., *Arch. Chem. Farm.* **3**, 109 (1936).

Turner, R. A., Huebner, C. F., and Scholz, C. R., *J. Am. Chem. Soc.* **71**, 2801 (1949).

von Braun, J., Petzold, A., and Seeman, J., *Chem. Ber.* **55B**, 3779 (1922).

von Braun, J., Gmelin, W., and Schultheiss, A., *Chem. Ber.* **56B**, 1338 (1923).

von Braun, J., Gmelin, W., and Petzold, A., *Chem. Ber.* **57B**, 382 (1924).

Walker, G. N., *J. Org. Chem.* **27**, 2966 (1962).

Walker, G. N., and Weaver, B. N., *J. Org. Chem.* **26**, 4441 (1961).

Walters, L. R., Podrebarac, E. G., and McEwen, W. E., *J. Org. Chem.* **26**, 1161 (1961).

Wempen, I., Brown, G. B., Ueda, T., and Fox, J. J., *Biochemistry* **4**(1), 54 (1965).

Wenkert, E., and Wickberg, B., *J. Am. Chem. Soc.* **87**, 1580 (1965).

Wibaut, J. P., and Proost, W., *Rec. Trav. Chim.* **52**, 333 (1933).

Willstätter, R., and Jaquet, D., *Chem. Ber.* **51**, 767 (1918).

Willstätter, R., and Waldschmidt-Leitz, E., *Chem. Ber.* **54B**, 113 (1921).

Witkop, B., *J. Am. Chem. Soc.* **70**, 2617 (1948).

Woodward, R. B., and Doering, W. E., *J. Am. Chem. Soc.* **67**, 860 (1945).

Yakhontov, L. N., Yatesenko, S. V., and Rubtsov, M. V., *Zh. Obshch. Khim.* **28**, 3115 (1958).

Yamamoto, K., *Yakugaku Zasshi* **76**, 922 (1956).

Young, D. V., and Snyder, H. R., *J. Am. Chem. Soc.* **83**, 3160 (1961).

Yur'ev, Yu. K., and Shen'yan, F. F., *Zh. Obshch. Khim.* **4**, 1258 (1934).

23

Hydrogenation of Acid Chlorides— Rosenmund Reduction

Selective hydrogenation of an acid chloride to an aldehyde is known as the Rosenmund reduction:

$$RCOCl + H_2 \longrightarrow RCHO + HCl$$

This useful reduction was reviewed thoroughly in 1948 by Mosettig and Mozingo. The review included a discussion of the scope and limitations of the reaction, the experimental procedure, and a comprehensive tabular survey of the acid chlorides that had been reduced. The catalysts used up to that time for these reductions were with few exceptions palladium, and this overwhelming preference for palladium has continued to date.

The central problem in the reduction revolves around the fact that the aldehyde itself can be reduced to the alcohol or hydrocarbon:

$$RCHO + H_2 \longrightarrow RCH_2OH$$
$$RCH_2OH + H_2 \longrightarrow RCH_3 + HOH$$
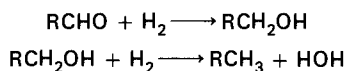
These reactions represent yield losses per se and the products, water and alcohol, decrease the yield still further by interaction with the acid chloride.

I. CATALYST REGULATORS

Much attention has been given to the problem of permitting reduction to the aldehyde while inhibiting further hydrogenation. Many investigators have used so-called catalyst regulators, such as quinoline-sulfur, thiourea, thiophene, etc., but these are not always needed and are apparently sometimes harmful. Some of the conflicting reports in the literature may arise from the fact that the solvent itself may contain enough impurities to act as an inhibitor. For instance, good yields of aldehyde were obtained without added poison with technical xylene as a solvent, but when the xylene was purified by distillation over aluminum chloride the yield of aldehyde was

very low (Zetzsche and Arnd, 1926). Because of the possibility of inadvertent and uncontrolled poisoning, it has been suggested that a poison be used to ensure uniform reaction conditions (Hershberg and Cason, 1955).

A study has been made of the mechanism of poisoning in the Rosenmund reduction over palladium-on-barium sulfate. Benzoyl chloride was the model substrate and tetramethylthiourea, thiourea, thiophene, and dibenzo-thiophene the poisons investigated. The yield of benzaldehyde increased as the amount of poison increased, and the effectiveness of these poisons, on a molar basis, decreased in the order given above. Tetramethylthiourea was very much more effective than dibenzothiophene. There was no clear correlation between the size of the poisoning molecule and its effectiveness. Sulfur could be made to function as an effective poison only if it were added to the reaction mixture at reflux temperature, a fact that led to the suggestion that the effective poison was palladium sulfide, but this was disproved (Affrossman and Thomson, 1962).

Benzyl alcohol was shown to arise in this reaction through hydrogenation of intermediate benzaldehyde and not directly from benzoyl chloride:
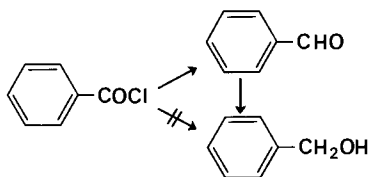
To account for the increased yields of aldehydes obtained in the presence of poisons, it was postulated that hydrogenolysis of benzoyl chloride requires only dual catalyst sites, whereas hydrogenation of the aldehyde requires quadruple sites. The addition of poisons decreases the number of quadruple sites much more rapidly than the number of dual sites (Affrossman and Thomson, 1962). Benzaldehyde may also be obtained in excellent yield by hydrogenation over regulated platinum oxide. The reduction is exceptionally sensitive to the catalyst inhibitor; catalysts modified by thiourea gave excellent results, but numerous other sulfur and nitrogen compounds proved unsuitable as regulators (Weygand and Meusel, 1943).

II. SIDE-REACTIONS

Various other side-reactions in addition to formation of alcohols and hydrocarbons may occur in a Rosenmund reduction. Carbon monoxide may be lost according to the overall equation:

$$RCOCl + H_2 \longrightarrow RH + CO + HCl$$
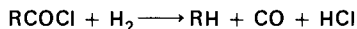
In certain cases, as with triphenylacetyl chloride, this reaction is quantitative (Rosenmund and Zetzsche, 1921). Carbon monoxide can be lost after the aldehyde is formed; palladium makes an excellent catalyst for decarbonylation of aldehydes (Copelin and Garnett, 1959; Hoffman *et al.*, 1962):
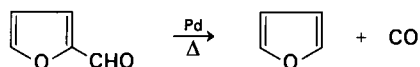
Dimerized products may occur, as in the reduction of diphenylacetyl chloride over poisoned 5% palladium-on-barium sulfate; this reduction is, however, unusual (Burr, 1951):

$$(C_6H_5)_2CHCOCl \longrightarrow (C_6H_5)_2CHCH(C_6H_5)_2 + (C_6H_5)_2CH_2 + (C_6H_5)_2CHCOOH$$
$$\qquad\qquad (47\%) \qquad\qquad (13.5\%) \qquad\quad (13.5\%)$$
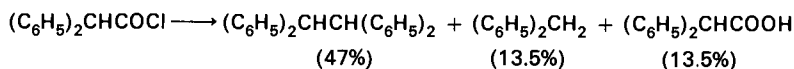
Tetraphenylethane is believed to be formed by the sequence: diphenylacetyl chloride → diphenylchloromethane → tetraphenylethylene → tetraphenylethane. In contrast to the above reaction, diphenylpropionyl chloride is converted smoothly to diphenylpropionaldehyde over quinoline–sulfur-poisoned 5% palladium-on-barium sulfate, a reaction that is said to offer the best route to this aldehyde (Harsanyi *et al.*, 1964):

$$(C_6H_5)_2CHCH_2COCl \longrightarrow (C_6H_5)_2CHCH_2CHO$$

III. PROCEDURE

The reduction is usually carried out in refluxing solvent, frequently xylene or toluene, but the best yields of aldehyde are reported to be obtained if the temperature is kept near the lowest point at which hydrogen chloride is evolved (Boehm and Schumann, 1933). If the reduction is carried out at reduced pressure, refluxing, which assists in removal of hydrogen chloride, occurs at lower temperatures. In this way I was converted in refluxing benzene to the dialdehyde (II) via the acid chloride in 92–94% yield by unpoisoned 10% palladium-on-carbon at 30–35°C. Conventional Rosenmund conditions proved too vigorous and failed to give good results (Johnson *et al.*, 1957). The chlorides of dibasic acids ordinarily do not give good yields of dialdehydes (Mosettig and Mozingo, 1948).
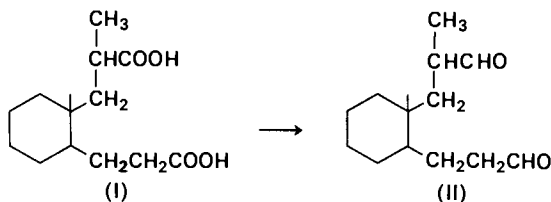
Foye and Lange (1956) reported that, in reduction of α-phthalimido acid chlorides to the aldehyde, a nonpoisoned 10% palladium-on-carbon catalyst was more effective than the conventional poisoned catalysts. Yields of pure aldehyde up to 95% were obtained with no evidence of reduction to alcohol. Three different procedures, all successful, were used in these reductions. In one procedure, hydrogen was bubbled into a stirred suspension of the catalyst and substrate in benzene at reflux temperature. In a modification, the solution was refluxed under reduced pressure at 38–40°C; this technique shortened the reaction time appreciably. The third method consisted in carrying out the reduction in ethyl acetate with dimethylaniline as hydrogen chloride acceptor. The procedure for preparation of 3,4,5-trimethoxy-benzaldehyde, as given by Huang et al., (1948), will serve as an illustration of how a Rosenmund reduction may be carried out. Several earlier pro-cedures for preparation of this material by Rosenmund reduction of tri-methoxybenzoyl chloride (Späth, 1919; Slotta and Heller, 1930; Mauthner, 1931; Nierenstein, 1931) were found to be erratic and at times to give almost none of the desired product. A 500-ml three-necked flask with ground-glass joints was fitted with a Hershberg stirrer sealed with rubber tubing, a reflux condenser, and a gas inlet tube with a 10-mm diameter sintered glass disc of medium mesh extending as low as possible without touching the stirrer. The flask was charged with 65 gm 3,4,5-trimethoxybenzoyl chloride (pre-pared from 3,4,5-trimethoxybenzoic acid and phosphorus pentachloride and distilled twice at 1 mm pressure), 230 ml xylene (dried by distillation over sodium), 20 gm palladium-on-barium sulfate (prepared according to the directions of Mozingo, (1955), and 1 ml stock poison (Nierenstein, 1931). The top of the condenser was connected by glass tubing to an inverted funnel, which dipped just below the surface of 50 ml of water contained in a 500-ml beaker. Commercial electrolytic hydrogen, dried over concentrated sulfuric acid, was passed into the reaction mixture at such a rate that about one bubble emerged from the inverted funnel every 8 seconds. After the air had been replaced by hydrogen, heating by means of a Glas-col mantle was begun, the stirrer started, and the mixture brought to gentle reflux. The course of the reduction was followed through measurement of the evolved hydrogen chloride by running 2 N alkali solution into the beaker at a con-venient rate. After 3 hours, 95% of the theoretical hydrogen chloride had been evolved and the reduction was stopped. The aldehyde was obtained through its bisulfite addition compound in 60–64% yield. Larger batches gave comparable yields. The aldehyde was obtained in 81% yield by re-duction of the acid chloride over sulfur–quinoline-regulated palladium-on-barium sulfate, but the experimental procedure for this preparation is sketchy (Rapoport et al., 1951). Benington and Morin (1951), repeating the procedure of Slotta and Heller (1930), obtained the aldehyde in 59% yield.

Detailed experimental directions for carrying out a Rosenmund reduction

of mesitoyl chloride over unregulated palladium-on-barium sulfate (Barnes, 1955) and β-naphthoyl chloride over quinoline–sulfur-regulated palladium-on-barium sulfate (Hershberg and Cason, 1955) have been given in *Organic Syntheses*. The reduction of mesitoyl chloride does not require a stirrer, but without a stirrer the reaction time is increased three-fold. It has been recommended that a tantalum Hershberg stirrer be used instead of a glass stirrer to minimize the chance of breakage (Mosettig and Mozingo, 1948). Commercial electrolytic hydrogen used directly from the cylinders without purification is generally satisfactory.

IV. SELECTIVE HYDROGENATION

Preferential hydrogenation of acid chlorides to aldehydes has been carried out in the presence of a number of other functional groups with varying degrees of success. Aromatic halogens apparently survive the reduction without extensive loss. The acid chlorides from 4,6-dichloropyridine-2-carboxylic acid, 5,6-dichloropyridine-3-carboxylic acid, and 2,6-dichloropyridine-4-carboxylic acid were reduced in xylene over unregulated palladium-on-barium sulfate in 50–60% yield based on the acid (Graf and Weinberg, 1932). Reduction of *o*-chlorobenzoyl chloride in toluene over 2% palladium-on-kieselguhr regulated by quinoline–sulfur afforded *o*-chlorobenzaldehyde in 70% yield (Rosenmund and Zetzsche, 1921). A 60% yield, based on the acid used, of *m*-fluorobenzaldehyde was obtained by hydrogenation of the corresponding acid chloride in xylene over unregulated palladium-on-barium sulfate (Shoesmith *et al.*, 1926). Hydrogenation of 4-chloro- and 6-chloro-1-naphthoyl chloride over 5% palladium-on-barium sulfate modified by quinoline–sulfur afforded the corresponding aldehydes in 73% and 63% yields based on the acid (Jacobs *et al.*, 1946).

Both the aromatic nitro function and carbon–carbon double bond have emerged unchanged in Rosenmund reactions over regulated palladium catalysts. These are quite remarkable examples of selectivity, inasmuch as palladium is among the most active catalysts known for reduction of olefins and nitro compounds. *p*-Nitrobenzaldehyde was obtained in 91% yield by hydrogenation of *p*-nitrobenzoyl chloride over 2% palladium-on-kieselguhr modified by quinoline–sulfur; unregulated catalysts gave undefined products, presumably because of reduction of the nitro function (Rosenmund and Zetzsche, 1921). Reduction of cinnamoyl chloride over quinoline–sulfur-regulated palladium-on-barium sulfate at 122°C (560 mm Hg) afforded cinnamaldehyde in 56% yield; when regulated by thioquinanthrene the yield was 60% (Rosenmund and Weiler, 1923). If the carbon–carbon double bond is highly substituted, it evidently will survive a Rosenmund reduction

over unregulated catalyst. For instance, 3-(4-methylcoumarinyl)formyl chloride was converted to 3-formyl-4-methylcoumarin over palladium-on-barium sulfate in refluxing xylene (Schroeder and Link, 1953).

A series of ω-fluoroaldehydes was prepared by reduction of the corresponding acid chlorides over poisoned palladium-on-barium carbonate in boiling xylene, using oxygen-free hydrogen. The highly variable yields were attributed to the changing quality of the catalyst and to the instability of the product (Wilshire and Pattison, 1956). Attempts to prepare chloral by reduction of trichloroacetyl chloride over poisoned palladium-on-barium sulfate were unsuccessful. The product was dichloroacetyl chloride, isolated in 50–60% yield; no chloral was found (Sellers and Bissinger, 1954):

$$Cl_3CCOCl \quad \begin{array}{c} \xrightarrow{\quad\times\quad} Cl_3CHO + HCl \\ \xrightarrow{\qquad} Cl_2HCOCl + HCl \end{array}$$
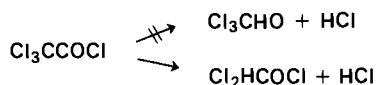
Difluorochloroacetyl chloride, on the other hand, undergoes a Rosenmund reduction smoothly to give difluorochloroacetaldehyde in 87% yield (Woolf, 1959).

The cyano function of p-cyanobenzoyl chloride survived a Rosenmund reduction in xylene over poisoned palladium-on-barium sulfate, and p-cyanobenzaldehyde was isolated in 63% yield (Rapoport et al., 1953):

$$H_2 + NC-\langle\!\bigcirc\!\rangle-COCl \longrightarrow NC-\langle\!\bigcirc\!\rangle-CHO + HCl$$
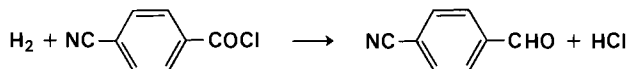
Ketonic acid chlorides have also been used in the Rosenmund reduction as a step in a simple synthesis of "queen substance" (Jaeger and Robinson, 1961):

$$H_2 + CH_3CO(CH_2)_5COCl \longrightarrow CH_3CO(CH_2)_5CHO + HCl$$
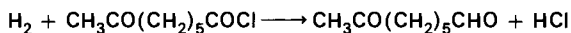
REFERENCES

Affrossman, S., and Thomson, S. J., *J. Chem. Soc.* p. 2024 (1962).

Barnes, R. P., *In* "Organic Syntheses," (Horning, E. C., ed.) Collected Vol. III, p.551. Wiley, New York, 1955.

Benington, F., and Morin, R. D., *J. Am. Chem. Soc.* **73**, 1353 (1951).

Boehm, T., and Schumann, G., *Arch. Pharm.* **271**, 490 (1933).

Burr, J. G., Jr., *J. Am. Chem. Soc.* **73**, 3502 (1951).

Copelin, H. B., and Garnett, D. I., U.S. Patent 3,007,941, Dec. 31, 1959.

Foye, W. O., and Lange, W. E., *J. Am. Pharm. Assoc. Sci. Ed.* **45**, 742 (1956).

Graf, R., and Weinberg, A., *J. Prakt. Chem.* **134**, 177 (1932).

Harsanyi, K., Korbonits, D., and Kiss, P., *J. Med. Chem.* **7**, 623 (1964).

Hershberg, E. B., and Cason, J., *In* "Organic Syntheses," (Horning, E. C., ed.) Collected Vol. III, p. 627. Wiley, New York, 1955.

Hoffman, N. E., Kanakkanatt, A. T., and Schneider, R. F., *J. Org. Chem.* **27**, 2687 (1962).

Huang, H. T., Tarbell, D. S., and Arnstein, H. R. V., *J. Am. Chem. Soc.* **70**, 4181 (1948).

Jacobs, T. L., Winstein, S., Henderson, R. B., Bond, J., Ralls, W., Seymour, D., and Florsheim, H., *J. Org. Chem.* **11**, 229 (1946).

Jaeger, R. H., and Robinson, R., *Tetrahedron* **14**, 320 (1961).

Johnson, W. S., Martin, D. G., Pappo, R., Darling, S. D., and Clement, R. A., *Proc. Chem. Soc.* p. 58 (1957).

Mauthner, F., *J. Prakt. Chem.* **129**, 281 (1931).

Mosettig, E., and Mozingo, R., *Org. Reactions* **4**, 362 (1948).

Mozingo, R., *In* "Organic Syntheses," (Horning, E. C., ed.) Collected Vol. III, p. 685. Wiley, New York, 1955.

Nierenstein, M., *J. Prakt. Chem.* **132**, 200 (1931).

Rapoport, H., Williams, A. R., and Cisney, M. E., *J. Am. Chem. Soc.* **73**, 1414 (1951).

Rapoport, H., Williams, A. R., Lowe, O. G., and Spooncer, W. W., *J. Am. Chem. Soc.* **75**, 1125 (1953).

Rosenmund, K. W., and Weiler, G., *Chem. Ber.* **56B**, 1481 (1923).

Rosenmund, K. W., and Zetzsche, F., *Chem. Ber.* **54B**, 425 (1921).

Schroeder, C. H., and Link, K. P., *J. Am. Chem. Soc.* **75**, 1886 (1953).

Sellers, J. W., and Bissinger, W. S., *J. Am. Chem. Soc.* **76**, 4486 (1954).

Shoesmith, J. B., Sosson, C. E., and Slater, R. H., *J. Chem. Soc.* p. 2760 (1926).

Slotta, K. H., and Heller, H., *Chem. Ber.* **63B** 3029 (1930).

Späth, E., *Monatsh. Chem.* **40**, 129 (1919).

Weygand, C., and Meusel, W., *Chem. Ber.* **76B**, 503 (1943).

Wilshire, J. F. K., and Pattison, F. L. M., *J. Am. Chem. Soc.* **78**, 4996 (1956).

Woolf, C., U.S.Patent 2,870,213, Jan. 20, 1959.

Zetzsche, F., and Arnd, O., *Helv. Chim. Acta* **9**, 173 (1926).

24

Catalytic Dehalogenation

Catalytic dehalogenation is a convenient way of removing halogen under mild conditions. Aryl halides are reduced in acidic, neutral, or alkaline media; aliphatic halides, unless activated by adjacent unsaturation, are reduced very slowly, if at all, in neutral or acidic media, but are reduced rapidly in basic solution. Bases of various kinds are often used in dehydro-halogenations. Base was originally used to prevent disintegration of the calcium carbonate support by the liberated halogen acid (Busch and Stöve, 1916), but its use has continued with catalysts quite stable to acid, for bases may accelerate the rate of dehydrohalogenation (Busch and Stöve, 1916; Mladenovic, 1933) and may also alter the selectivity of reduction (Reinecke, 1964).

I. CATALYSTS

Platinum metals differ widely in effectiveness in catalytic dehalogenations. Table I shows the rates of hydrogenolysis of benzyl chloride over 5% palladium-, platinum-, and rhodium-on-carbon in several solvents (South-wick, 1962). In many reductions the rate constantly decreased, and for this reason an average rate to 50% of completion, except for the slowest re-ductions, is tabulated. A constantly decreasing rate in hydrogenolysis of benzyl compounds has been reported before, and might be due to inhibition by toluene (Meschke and Hartung, 1960) or hydrogen chloride (Baltzly and Phillips, 1946) among other reasons. Palladium is by far the most active catalyst in all solvents. Platinum and rhodium are much less active, and their use is indicated in reduction of compounds containing benzyl halogen when dehalogenation is to be minimized. The rates of reduction of benzyl chloride vary markedly with the solvent as well as the catalyst. Extremely fast rates were obtained, surprisingly, over palladium in ethyl acetate. This solvent has been used infrequently in catalytic dehalogenations and perhaps warrants more attention.

TABLE I

HYDROGENOLYSIS OF BENZYL CHLORIDE[a]

Solvent	Average rate to 50% completion[b] (ml H_2/minute) using the following catalysts:		
	5% Pd/C	5% Pt/C	5% Rh/C
H_2O	40	10	4
$H_2O + HClO_4$ (1%)	60	15	6
$CH_3COOC_2H_5$	100	4	2
$CH_3COOC_2H_5 + HClO_4$ (1%)	120	6	5
CH_3COOH	50	5	5
$CH_3COOH + NaOCOCH_3$	120	40	16
CH_3OH	40	30	15
$n\text{-}C_6H_{14}$	20	1	0

[a] Each experiment was done with 4.5 ml benzyl chloride, 100 ml solvent, and 500 mg 5% metal-on-carbon at atmospheric pressure and room temperature.

[b] Except very slow reductions.

Table II shows the rates of hydrogenolysis of chlorobenzene over 5% palladium-, platinum-, and rhodium-on-carbon in several solvents (Hasbrouck, 1966). Palladium is the most active catalyst in each solvent system. Very large increases in rate can be obtained by addition of sodium acetate to acetic acid. Smaller increases are obtained by addition of sodium hydroxide to ethanol, and this base is actually detrimental to the rhodium catalyst. Platinum and rhodium are relatively ineffective, and their use is indicated in reduction of compounds containing aryl halogen when dehalogenation is to be minimized. In fact, these catalysts have already proved suitable for reductions of this type.

TABLE II

HYDROGENATION OF CHLOROBENZENE[a]

(average rate in ml H_2/minute)

Catalyst	Acetic acid	Acetic acid–sodium acetate	Ethanol	Ethanol–sodium hydroxide
5% Pd/C	4	55	25	100
5% Pt/C	3	45	5	8
5% Rh/C	1	11	7	4

[a] Each experiment was done with 50 ml solvent, 500 mg 5% metal-on-carbon catalyst, 0.0476 mole of chlorobenzene, and 0.1 mole of base (if used) at atmospheric pressure and room temperature. Many of the rates slowly declined as the reaction progressed. The reported rate is the average rate to 30% completion, except for the slowest reductions. Over platinum and rhodium in acetic acid–sodium acetate, the reduction continued at a slow rate after theoretical absorption for complete hydrogenolysis.

A. Amount of Catalyst

The extent of dehalogenation relative to reduction of other functions may be influenced by the amount of catalyst. In reduction of 1-halobenzoyl-2-isopropylidenehydrazines (Freifelder et al., 1961) and p-chloronitrobenzene (Rylander et al., 1965), reactions in which the halogen was to be retained, dehalogenation increased as the amount of catalyst was increased.

B. Synergism

An interesting promoting effect occurred in dehalogenation of 2,6-dichloro-3-cyclopentyl-5-methylpyridine over palladium catalysts. The addition of traces of platinum oxide, itself inactive in this reduction, to palladium chloride during preparation of the catalyst so increased the activity of the catalyst that the reduction was completed within minutes instead of hours (Pickard and Lochte, 1947). This promoting effect is similar to that found by Skita and Meyer (1912).

II. DEHALOGENATION IN BASIC MEDIA

The rate and also the products of a hydrogenation may be altered by the presence of small amounts of acids or bases. Bases are used frequently in catalytic dehalogenations, but whether the observed, often marked, effect of base on the reduction is brought about by the base itself, or by its action in neutralizing the liberated acid, or both, is not usually clear. Nor is it usually clear whether the base (or acid) functions by altering the catalyst or the substrate or both. Empirically it has been found that various bases are not always interchangeable, and the results may depend to a large extent on the base employed.

Reinecke (1964) has attempted to elucidate the function of base in the catalytic dehalogenation of aliphatic halides, using potassium hydroxide and triethylamine, bases of widely different character. Two model substrates, 2-dichloromethyl-2-methylcyclohexanone (I) and 4-dichloromethyl-4-methylcyclohexanone (V), were each reduced over 10% palladium-on-carbon in methanol containing triethylamine or potassium hydroxide. With the 2-substituted ketone (I) the major difference was in the rates of reduction, complete reduction to II requiring about 4 times as long in triethylamine as in potassium hydroxide solution. The initial rates in the two systems were equal, but in the presence of triethylamine the rate steadily decreased as the reaction progressed. This suggested to Reinecke that poisoning of the catalyst by triethylamine was not responsible for the declining rate, but poisoning

by a product of reduction could be, and he ascribed dissimilar actions to the two bases. Reduction of the 2-isomer in potassium hydroxide solutions also afforded some 6-methylheptanoic acid (IV), arising probably by reduction of 7-chloro-6-methyl-6-heptenoic acid (III).
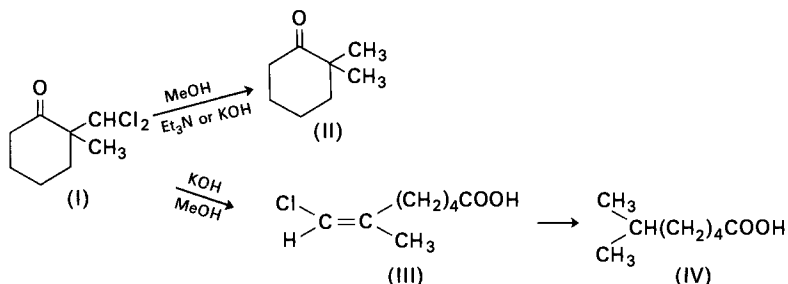
Dehalogenation of the 4-substituted ketone (V) in the presence of the two bases accentuated their differences more strongly. Reduction of V in the presence of potassium hydroxide afforded only dimethylcyclohexanone (VI), whereas in the presence of triethylamine the product was about two thirds VI and one third 4-dichloromethyl-4-methylcyclohexanol (VII). The formation of VII is anomalous, in that under these conditions carbonyl reduction would not be expected whereas hydrogenolysis of the chlorine atoms would. The dichloro alcohol (VII) was readily dehalogenated in the presence of potassium hydroxide, indicating that the inertness of these halogen atoms in the triethylamine reduction depends on the presence of the amine. This is a particularly interesting observation, in that amines are usually effective promoters in dehalogenation reactions. These unusual results were explained in terms of intermolecular interactions involving the chlorine and oxygen atoms and the amine (Reinecke, 1964).
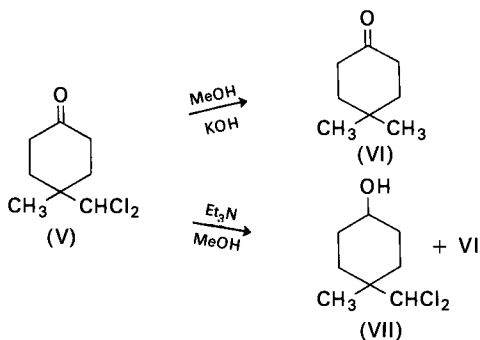
III. CHOICE OF BASE

A variety of bases have been used in catalytic dehalogenations, neutralizing the halogen acid as it is formed. These include such substances as sodium,

potassium, calcium, and barium hydroxides, magnesium oxide, sodium acetate, amines, and ammonia. Various comparative experiments in which one base has proved superior to another are given in the literature, but generalities governing the optimum choice of base have yet to be made. Fortunately, it appears that the choice of base is not critical in many catalytic dehalogenations. Some reductions, on the other hand, are strongly influenced not only by the base employed but also by its quality. For instance, a successful synthesis of benzocyclobutene was achieved by catalytic hydrogenolysis of 1,2-diiodobenzocyclobutene over 10% palladium-on-carbon in ethanol containing sodium ethoxide. The use of a freshly prepared sodium ethoxide gave yields of 20–38%, but when a pale orange sodium ethoxide, somewhat decomposed by aging, was used, the yields rose to 49–55%. The authors suggested that the improved yields arose through partial poisoning of the catalyst. The use of pyridine, sodium carbonate, or sodium hydroxide in place of sodium ethoxide gave yields below 20% (Cava and Napier, 1958).

A. Oxides and Hydroxides

Magnesium oxide is frequently used in catalytic dehalogenations. It seems to serve several functions. Apart from its role as a halogen acid acceptor, it has proved useful in limiting the depth of hydrogenation. For example, reduction of 2,4,6-trichloropyrimidine in the presence of sodium acetate afforded a tetrahydropyrimidine, but in the presence of magnesium oxide the pyrimidine was obtained (Whittaker, 1950). Similarly, reduction of 2,4-dichloropyrimidine over palladium-on-carbon in ethanol–water in the presence of freshly ignited magnesium oxide afforded pyrimidine (Whittaker, 1953), whereas reduction of a dichloroalkylpyrimidine over palladium-on-barium sulfate in butanol in the presence of barium hydroxide afforded the alkyltetrahydropyrimidine. Quite the reverse situation has also been reported; in the presence of magnesium oxide ring reduction occurred, but not in its absence. Catalytic dehalogenation of 6-chloro-4,5-diamino-pyrimidine over 5% palladium-on-carbon in the presence of magnesium oxide did not cease after absorption of one equivalent of hydrogen, but the reduction ceased spontaneously at theoretical absorption in water without added base (Bendich et al., 1954).

A typical experimental procedure for dehalogenation in the presence of magnesium oxide is illustrated by a new synthesis of 3-methyl-4-carbethoxy-pyrrole (IX), which afforded the product in greatly increased yield. A mixture

of 8 gm magnesium oxide, 0.1 mole of the 2,5-diiodo compound (VIII), and 135 ml methanol were reduced over 10 gm 10% palladium-on-carbon (prepared from palladium chloride) for 48 hours, at which time 0.2 mole of hydrogen had been absorbed. The catalyst was removed by filtration after a little sodium bisulfite had been added to the reaction mixture to prevent reoxidation of the iodide ion. The product (IX) was obtained in
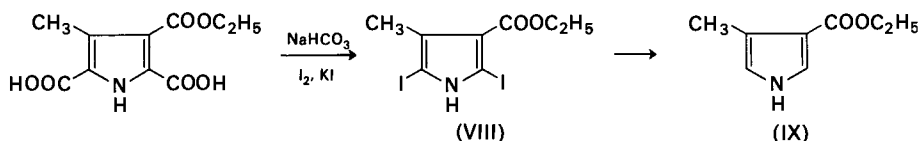
86% yield (Kleinspehn and Corwin, 1953). In a hydrogenation under similar conditions, 2-iodo-3-methyl-4-carbethoxy-5-formylpyrrole was dehalogenated without loss of the carbonyl function (Corwin and Kleinspehn, 1953):
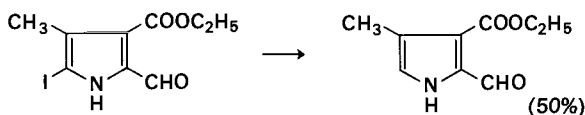
1. *Amount of Base*

Spiegler (1963) observed that the function of magnesium oxide may depend on its amount. Magnesium oxide present in 0.1–1.0% by weight, based on substrate, inhibits dehalogenation during reduction of halonitrobenzenes; less magnesium oxide is without effect, and more promotes dehalogenation. Similarly, small amounts of calcium hydroxide have been used to limit dehalogenation in reduction of halonitro compounds over rhodium catalysts (Dietzler and Keil, 1962). Ordinarily at least an equivalent of base per halogen atom is used when bases are employed at all.

The amount of potassium hydroxide employed in the selective reduction of 4,7-dichlorocarbostyril to 7-chlorocarbostyril had a marked effect on the yield:
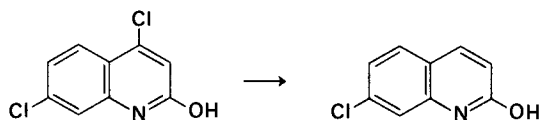
The maximum yield (93%) of 7-chlorocarbostyril was obtained with 1.25 equivalents of potassium hydroxide. One equivalent gave a 44.5% yield, 1.10 gave 59%, 1.35 gave 70.5%, and 2.0 or more equivalents gave only carbostyril. An excess of 0.25 equivalent of potassium hydroxide was needed

to prevent the product from precipitating. Raney nickel proved more selective than palladium-on-barium sulfate in this reduction (Lutz *et al.*, 1946).

2. *Batch Size*

The yield of product may depend on the batch size (Ross *et al.*, 1959). Hydrogenation of 5.8 mmoles of the pyrimidine (X) in 10 ml absolute ethanol containing 5.1 mmoles of magnesium oxide and 0.1 gm 5% palladium-on-carbon afforded XI in 51% yield. The reduction was allowed to proceed until it stopped spontaneously at 169% of the theoretical hydrogen absorption, which accounts in part for the modest yield. When the reduction was scaled up the yields were much lower, apparently due to reduction of the ring. It is not clear from the description of the experiment whether an effort was made to limit hydrogen absorption in the larger batch sizes. Hydrogenation of a similar compound (XII) gave XIII in 82.5% yield. In this reduction, hydrogen absorption ceased spontaneously at 112% of theory.

(X) X = NH$_2$
(XII) X = H

(XI) X = NH$_2$
(XIII) X = H
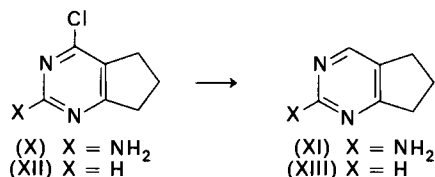
3. *Mode of Addition*

Overberger and Kogon (1954), working with 2,4-dichloro-6-methyl-pyrimidine (XIV), found the mode of addition of the reactants to be of importance. When the substrate was added to a mixture of magnesium oxide and methanol followed by water and catalyst, attempts to hydrogenate the mixture failed. The compound isolated was the 2,4-dimethoxy compound derived by displacement of the halogens. However, when the substrate was added to a mixture of magnesium oxide and water followed by methanol and 10% palladium-on-carbon, hydrogenation proceeded smoothly to afford 4-methylpyrimidine (XV), isolated by distillation in 30% yield. The

(XIV)

Pd/SrCO$_3$
H$_2$O-ether

Pd/C
CH$_3$OH

(XVI)

(XV)

same yields were obtained when the reduction was carried out in 27%
ammonium hydroxide and methanol or in ammoniacal methanol. Earlier
workers (Marshall and Walker, 1951) obtained 2-chloro-4-methylpyrimidine
(XVI) by carrying out the hydrogenation over palladium-on-strontium
carbonate with magnesium oxide and a 1:1 water–ether mixture.

B. AMINES AND AMMONIA

Amines and ammonia are known to increase the rate of catalytic dehalo-
genation and to decrease the rate of hydrogenation of a number of other
functions. Accordingly, they may be a useful type of base to employ in dehalo-
genations when a selectivity problem exists (see, however, Reinecke, 1964).
For instance, dehalogenation of 2′,3′-dideoxy-3′-iodouridine (XVII) occurred
rapidly over 10% palladium-on-carbon in 50% aqueous methanol containing
2.4 molar equivalents of triethylamine to afford, after recrystallization,
2′,3′-dideoxyuridine (XVIII) in 83% yield. In the absence of triethylamine,
almost complete reduction of the 5,6 double bond occurred (Pfitzner and
Moffatt, 1964). This procedure was found to be very much more convenient
and efficient than hydrogenation in the presence of ammonium hydroxide
(Michelson and Todd, 1955), as complete removal of the resulting ammonium
iodide was difficult.

(XVII)   (XVIII)

Aqueous alcoholic ammonia proved much superior to sodium hydroxide
in ethanol or to neutral ethanol for dehalogenation of 3,6-dichloropyridazine
to pyridazine. Reductions carried out in the presence of sodium hydroxide
afforded pyridazine in 28% yield after slow absorption of hydrogen, whereas
in ammonia solution the reduction was rapid and the yield was 61% after
distillation. Hydrogenation of a mixture of 29.6 gm 3,6-dichloropyridazine,
40 ml ammonium hydroxide (28%), and 2 gm 5% palladium-on-carbon

in 70 ml ethanol was complete in 45 minutes at 3 atm pressure (Mizzoni and Spoerri, 1951). On the other hand, dehalogenation of a more complex dichloropyridazine, i.e., 1-benzyl-4,7-dichloroimidazo[4,5-d]pyridazine, proceeded smoothly without debenzylation over 5% palladium-on-carbon in ethanol–sodium hydroxide (Carbon, 1958).

Amines have been used in conjunction with alkali in dehalogenation reactions. Isonicotinic acid esters were prepared in good yield by hydrogenolysis of the corresponding 2,6-dichloro compounds over 5% palladium-on-carbon at 50–60°C and 40 psig in a sodium hydroxide solution containing two equivalents of triethylamine (Bavley *et al.*, 1956).

IV. HALOGEN COMPOUNDS WITH OTHER FUNCTIONS

A frequent goal in catalytic dehalogenation is the removal of a halogen without concomitant reduction of other functions in the molecule. Whether this goal can be realized depends on the halogen, the other functions involved, and the overall structure of the substrate.

A. HALOKETONES

Dehydrohalogenation of the haloketones without reduction of the carbonyl is readily accomplished with palladium catalysts. This result could be anticipated in those instances where the carbonyl function is not activated by an adjacent aromatic system, for aliphatic ketones are reduced slowly over palladium. For example, reduction of 1-bromobicyclo[3.3.1]nonan-9-one over 1% palladium-on-calcium carbonate in ethanol containing sodium acetate smoothly removed the bromine without reduction of the ketone. The reduction stopped spontaneously (Cope and Gale, 1963).
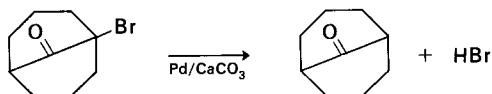
Similarly, reduction of a mixture of 50.0 gm 2-chloro-3-phenyl-2-cyclobutenone, 24 gm sodium acetate, 200 ml methanol, and 6.0 gm 20–30% palladium-on-carbon catalyst ceased spontaneously after many hours at 60 psig to afford 3-phenylcyclobutanone in 85–91% yield. Apparently little or none of the ketonic function was reduced (Manatt *et al.*, 1964).
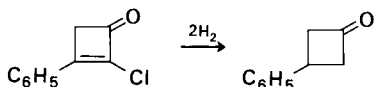
On the other hand, since aromatic ketones are readily reduced over palladium catalysts, it is not apparent that selective dehydrohalogenations can be achieved easily. In fact, however, there is apparently little difficulty. For instance, a 6-bromofluorenone was debrominated over prereduced palladium-on-barium sulfate catalysts in ethanol–water in the presence of potassium hydroxide without reduction of the ketone (Barnes and Gerber, 1961).
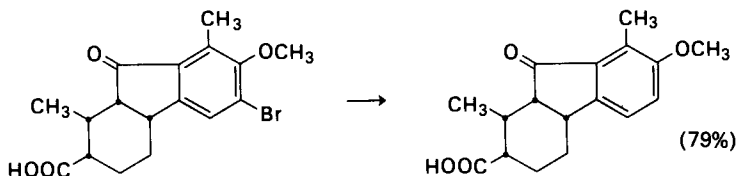
Hydrogenolysis of griseofulvic acid over 10% palladium-on-carbon in water containing sodium bicarbonate or triethylamine gave the dechloro-triketone (Arkley *et al.*, 1963).
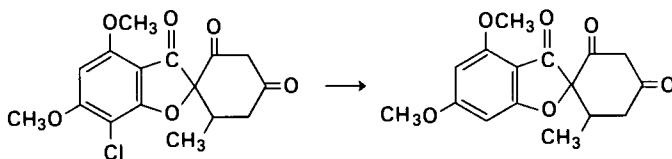
It may be necessary to interrupt the reduction after absorption of one equivalent of hydrogen if high selectivity is to be obtained. For example, reduction of XIX occurred very rapidly over 5% palladium-on-carbon and good yields of the debromo ketone (XX) could be obtained only by stopping the reduction after absorption of one mole of hydrogen. The solvent was 95% ethanol containing sodium acetate (Sargent and Agar, 1958).

(XIX)   (XX)
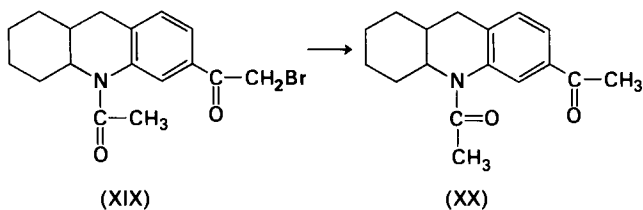
Huffman (1959) has pointed out that the use of aromatically bound chlorine is a potentially useful, but rarely used, means of blocking a reactive position on the aromatic nucleus. He made use of this blocking group in the synthesis of 5-methoxy-1-tetralone, through succinoylation of *p*-chloro-anisole, cyclization, and dehydrohalogenation. The hydrogenolysis, carried out over 10% palladium-on-carbon in ethanol containing an equivalent of triethylamine, proceeded smoothly and virtually ceased after absorption

of one mole of hydrogen. After recrystallization the tetralone was obtained in 53% yield.
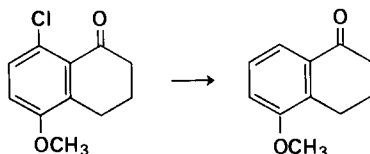
A study has been made on methods of minimizing dehydrohalogenation during reduction of 4-halo-2-acyl phenols to 4-halo-2-alkyl phenols over platinum black. The fluoro compounds were relatively stable to dehydrohalogenation, whereas the chloro compounds were sufficiently labile to require special techniques to minimize loss of chlorine. Selective hydrogenation was achieved by use of sulfuric acid as a specific activator. Table III shows how the yield and percent of dehydrohalogenation vary with the solvent. The rate of hydrogenation decreased with increasing molecular weight of the carboxylic acid solvent; perhaps the changes in yield and percent dehydrohalogenation may be correlated with hydrogen availability at the catalyst surface (Kindler *et al.*, 1953).

TABLE III

HYDROGENATION OF 4-CHLORO-2-ACETYLPHENOL

Solvent	Yield of 4-chloro-2-ethylphenol	Percent dehydro-halogenation
Benzene or cyclohexane	(no reduction)	—
Propanol	—	51
Acetic acid + sulfuric acid	70%	16.7
Propionic acid + sulfuric acid	75%	11.9
Butyric acid + sulfuric acid	75%	11.2
Caproic acid + sulfuric acid	85%	7.9

B. HALOOXIMES

Oximes may be obtained in excellent yield by dehydrohalogenation of halooximes. A selective removal of chlorine from 2-chlorocyclohexanone oxime to cyclohexanone oxime was achieved in 93% yield by reduction over 5% palladium-on-carbon in ethyl acetate containing sodium acetate (Belgian Patent 624,384):
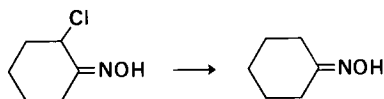
Dehydrohalogenation of 2-chlorocyclododecadien-5,9-one-1-oxime over palladium-on-alumina in methanol at room temperature and 3000 psig

gave cyclododecanone oxime in 89% yield; it is interesting that the oxime resists reduction under these high pressures (German Patent 1,162,359):
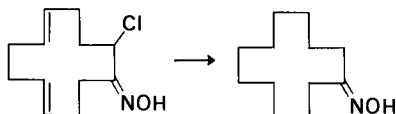
No examples were found of dehydrohalogenations of halooximes having the halogen more remote from the oxime function.

C. HALONITRILES

Dehydrohalogenation of aromatic halonitriles without simultaneous reduction of the nitrile apparently presents no special difficulties. An 87% yield of 3-cyano-4-methylpyridine was obtained by reduction of the corresponding 2,6-dichloro compound over unsupported palladium chloride in methanol containing two equivalents of anhydrous sodium acetate (Bobbitt and Scola, 1960):
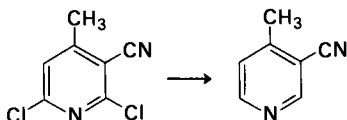
Similarly, ethyl 4,6-dimethylnicotinate was prepared by selective hydrogenation of 4,6-dimethyl-2-chloronicotinonitrile over 5% palladium-on-carbon in ethanol–water containing magnesium oxide, followed by hydrolysis, and esterification (Sperber, et al., 1959).

Both the halogen and nitrile may be reduced if the reduction is allowed to continue. The nitro function of XXI was selectively reduced over platinum oxide in 95% ethanol to give the corresponding amine (XXII) in 76% yield. Further reduction in acetic acid containing sodium acetate over a mixture of platinum oxide and 5% palladium-on-carbon removed the chlorine and converted the nitrile function to an amine (XXIII) (Harris and Folkers, 1939).

(XXI)   (XXII)   (XXIII)
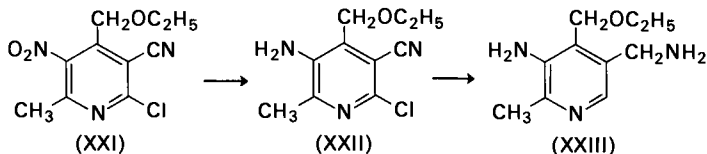
D. HALOHYDRINS

Since nonactivated alcohols are stable toward reduction over palladium catalysts, selective dehydrohalogenation of halohydrins is usually accomplished readily. For example, dehydrobromination of 2-bromopseudotropine

proceeded smoothly over palladium-on-carbon in absolute ethanol, to give pseudotropine; two parts of catalyst to one part of substrate was used in the reduction, which took 5 hours (Nickon, 1955):
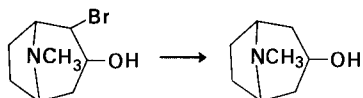
A more unexpected reduction of a bromohydrin is shown by the following examples, in which the different behavior of two bromohydrins of the 16-acetyl-5β-androstane series was of help in providing a structural assignment. On reduction over 25% palladium-on-calcium carbonate in methanol, XXIV lost only the halogen, but XXV, similarly treated, lost both the bromine and hydroxyl. The authors point out that in XXV the hydroxyl would be readily eliminated to form the easily hydrogenated 16,17 double bond (Taub et al., 1961).

(XXIV)

(XXV)
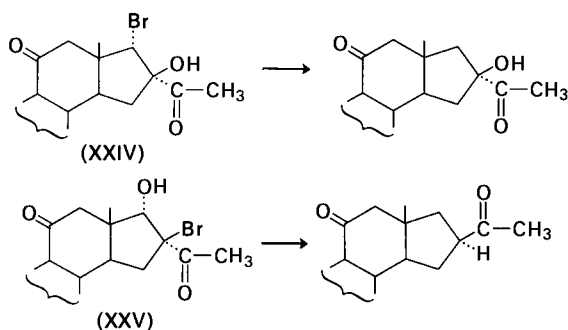
E. Aromatic Compounds

Halogens attached to carbocyclic aromatic rings are easily removed without, or prior to, reduction of the aromatic system (Blicke and McCarty, 1959). On the other hand, reduction of an aromatic ring with considerable retention of halogen is much more difficult. Reduction of fluorobenzene over platinum black led only to cyclohexane; the intermediate in the reduction was benzene and not fluorocyclohexane (Swarts, 1936). Reduction of o-fluorophenylphosphonic acid over 5% rhodium-on-alumina afforded hydrogen fluoride and pure cyclohexylphosphonic acid. However, dehalogenation of m-chlorophenylphosphonic acid did not proceed so smoothly; the rate of reduction of the aromatic ring was comparable to the rate of halogen removal, resulting in a mixture of products (Freedman et al., 1955). Reduction of chlorobenzene over 5% rhodium-on-carbon in methanol gave a mixture of cyclohexane and cyclohexyl chloride (Berkowitz and Rylander, 1958). Reduction of a carbocyclic aromatic ring with retention of aryl halogen is probably best achieved, if it can be at all, over rhodium catalysts.

Reduction of an aromatic ring may occur competitively with loss of non-aromatic halogen. Dehydrohalogenation of 2-chloro-N,N-diphenylacetamide to N,N-diphenylacetamide proceeded smoothly over 10% palladium-on-carbon in absolute ethanol, but erratically over platinum. When a platinum-catalyzed reduction was stopped after absorption of one equivalent of hydrogen, more than 60% of the starting material was recovered unchanged; presumably reduction of the aromatic amine had occurred (Schulenberg and Archer, 1965).
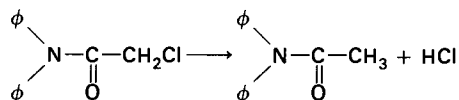
Heterocyclic aromatic systems are in general reduced more easily than carbocyclic systems, and ring saturation may follow dehalogenation if the reduction is not interrupted. In certain systems, ring saturation occurs at a rate comparable to dehydrohalogenation. Attempts to prepare 3-phenylcopyrine by dehydrohalogenation of the 1-chloro derivative were unsuccessful for this reason. Reduction over palladium chloride in methanol containing potassium acetate gave five products, on absorption of one mole of hydrogen. A mixture of products was also obtained on reduction over palladium-on-calcium carbonate in ethanol (Bobbitt and Doolittle, 1964).
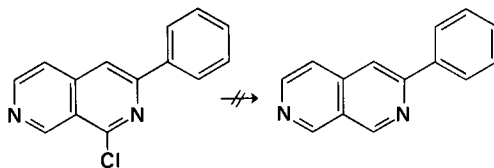
Certain heterocyclic systems may themselves undergo hydrogenolysis. Dehalogenation of 1-chloro-4-methylphthalazine (XXVI) proceeded smoothly over 10% palladium-on-carbon in ethanol–sodium·hydroxide but, over platinum oxide, cleavage of the nitrogen–nitrogen bond occurred. However, dehalogenation of 3-chloroindazole (XXVIa) over platinum oxide afforded indazole in good yield (Stephenson, 1963).

(XXVI)   (XXVIa)
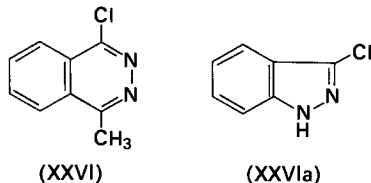
Halonitroaromatics

No example was found in which this type of compound was dehydrohalogenated without reduction of the nitro function. On the other hand,

dehydrohalogenation may or may not accompany reduction of the nitro function. If the halogen is to be removed, palladium is the preferred catalyst; if the halogen is to be retained, platinum or rhodium is more useful. (The reduction of these compounds is discussed at some length in the chapter on hydrogenation of the nitro group; a recent observation on control of selectivity not included therein is worth noting.) Dorfman *et al.* (1964) were able to obtain good yields of 2,5-dichloro-3-aminobenzoic acid by reduction of the ammonium or substituted ammonium salts of the corresponding nitro compound over palladium or platinum catalysts in water. Hydrogenolysis of the halogen was unimportant when the ammonium salts were used, but was extensive with alkali metal salts.
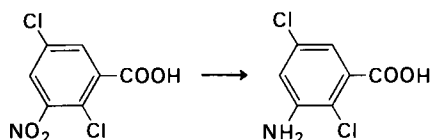
The degree of dehydrohalogenation of halonitro compounds may be controlled by the amount of catalyst. Dehydrohalogenation during reduction of the nitro function has been minimized by restricting the amount of catalyst to one part of platinum for every 10,000–100,000 parts of substrate and conducting the hydrogenation in the presence of a nitrogen base, such as morpholine (Kosak, 1964).

F. HALOOLEFINS

Haloolefins may be reduced at either one or both functions. Reduction of both functions presents no particular difficulty, for by employing a basic medium the halogen may be removed, even if the molecule becomes paraffinic prior to dehalogenation. For example, the vinylic and allylic halogens and the carbon–carbon double bond in XXVII were removed by hydrogenation over 5% palladium-on-carbon in tetrahydrofuran containing 1.0 *N* sodium hydroxide to afford XXVIII. Prior hydrolysis of the allylic halogen (XXIX) followed by hydrogenation gave XXX. The reduction proceeded at a constantly decreasing rate, which perhaps reflects a gradual transition of activated to nonactivated halogen (Bergman, 1963).
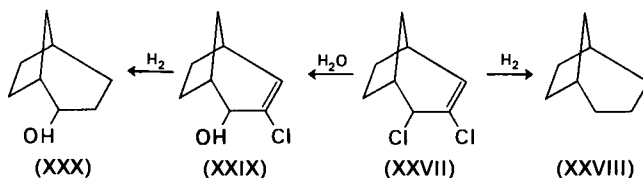
Selective reduction of haloolefins containing nonactivated halogen may be easily controlled by the presence or absence of base. The dichloromethyl ketone (XXXI) was saturated without dehalogenation when reduced over platinum oxide in methanol. The reduction stopped spontaneously and no appreciable loss of halogen was observed. Reduction of XXXI over palladium-on-barium sulfate in 10% alcoholic potassium hydroxide removed both halogens as well, to afford the saturated alcohol (XXXII) (Woodward, 1940).
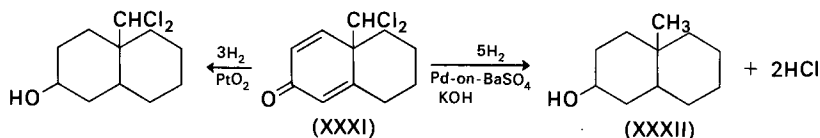
Hydrogenation of 2-chloro-3-phenyl-2-cyclobutenol (XXXIII) over 10% palladium-on-carbon in methanol containing sodium acetate gave *cis*-3-phenylcyclobutanol (XXXIV) in 92% yield. Apparently there was little if any hydrogenolysis of the allylic hydroxyl (Manatt *et al.*, 1964).
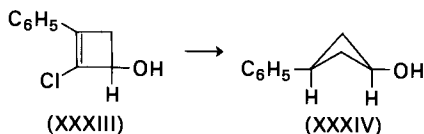
Dehalogenation in neutral solution of a halogen activated by an olefinic linkage implies that loss of halogen preceded olefin saturation. The dehalogenation and saturation of the vinyl chloride (XXXV) on reduction over platinum oxide in neutral ethanol may be so interpreted (Cristol and Hause, 1952).
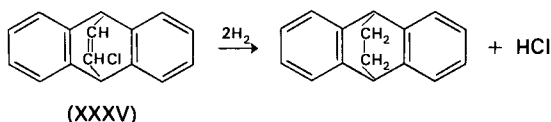
1. Catalyst and Solvent

The extent of dehalogenation occurring during hydrogenation of haloolefins may depend on the catalyst and solvent. Hydrogenation of 1,3-dichloropropene over platinum oxide and supported palladium and platinum catalysts afforded mainly propane and hydrogen chloride, whereas over rhodium catalysts good yields of 1,3-dichloropropane and propyl chloride were obtained. The yield of 1,3-dichloropropane obtained in reduction over rhodium-on-alumina varied markedly with the solvent. At constant conditions, 100°C and 400–600 psig pressure, the yield of dichloropropane was,

in cyclohexane, ether, ethanol, and acetic acid, 47.9%, 30.8%, 2.5%, and 2.5%, respectively (Ham and Coker, 1964).

The catalyst carrier also influenced the yields somewhat; in cyclohexane the yield of dichloropropane was 47.9% and 37.4% over rhodium-on-alumina and rhodium-on-carbon, respectively. Since 1,3-dichloropropane was shown to be stable under the conditions of the reaction, the varying yields are a reflection of the rate ratio of hydrogenation of the carbon–carbon double bond and hydrogenolysis of the allyl and vinyl halogen.

A report has been made of a palladium-on-carbon catalyst, prepared by reduction of palladium chloride in the presence of activated charcoal, which, although inactive for reduction of allyl bromide, readily catalyzed reduction of 2-bromopropene and 2,3-dibromopropene. The authors concluded from these experiments that this palladium catalyst was specific for the conversion:

$$-\overset{|}{\underset{|}{C}}-C(Br) = C- \longrightarrow -\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-$$
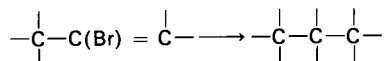
This catalyst was employed in the hydrogenation of a compound suspected of being 5-(α-bromopropylidene)hydantoin, and its successful reduction suggested to the authors the presence of the vinyl and not allyl bromide grouping (McMullen *et al.*, 1954). Interpretations of this type are fraught with uncertainties.

2. Preferential Dehalogenation of Haloolefins

Of more interest and rarity are those catalytic dehalogenations of haloolefins in which the olefinic function survives. Examples of this type might be expected to be most prevalent in compounds in which the olefin is or becomes sterically hindered, or in compounds in which for other reasons the olefin is particularly resistant to reduction. An example of the latter type is the reductive transformation of 5-chloro-2β-dinitrostyrene to indole, a compound reduced with some difficulty. The goal of the reduction, 5-chloroindole, was not realized, as the halogen was lost during the reduction (Benington *et al.*, 1960). This result is in accord with the facile hydrogenolysis of 2- or 4-chloronitrobenzene over palladium or platinum (a reaction discussed further in the chapter on nitro group hydrogenation).
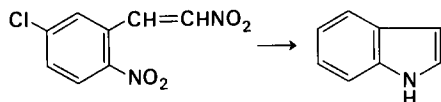
An intriguing example of the preservation of a double bond during dehydrohalogenation is found in the work of Conroy (1955) on 14-bromocodeinone (XXXVI). Catalytic hydrogenation of 14-bromocodeinone over 10% palladium-on-carbon in chloroform containing 5–10% of methanol ceased, after absorption of one equivalent of hydrogen, to afford the base

(XXXVII). Formation of XXXVII involves an unexpected migration of a double bond conjugated with a carbonyl to a position removed from the carbonyl with the consequent loss of resonance stabilization. Small amounts of methanol had a marked effect on this hydrogenation. A few reductions in which chloroform and/or benzene was used as a solvent proceeded very slowly, and ceased after a few percent of one equivalent of hydrogen had been absorbed. Addition of about 7% of methanol to these reductions caused the reaction to start again at a rapid rate, but no further increase in rate occurred on addition of more methanol. Catalytic hydrogenation of XXXVI over palladium-on-carbon in acetic acid resulted in absorption of two equivalents of hydrogen and afforded dihydrocodeinone in poor yield.

(XXXVI)   (XXXVII)
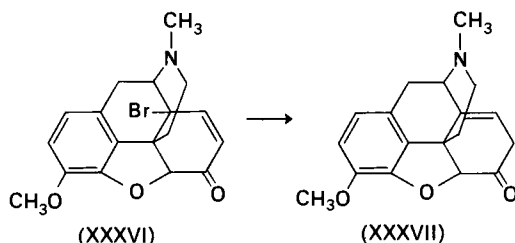
Esters of angelic acid were prepared in high yield by selective debromination of the corresponding 3-bromoangelate esters over 10% palladium-on-carbon inhibited by excess triethylamine. The catalyst used in the reduction was a commercial preparation, which before use was allowed to stand about 5 minutes in 10% potassium hydroxide. The catalyst was then filtered, washed successively with ethanol, water, ethanol, and ether, and then dried under reduced pressure. The reduction was carried out at atmospheric pressure with one part of catalyst, treated as above, and 10 parts of bromo ester in 20 parts of ethanol containing a 2–6 molar excess of triethylamine. All reductions were terminated after absorption of one equivalent of hydrogen. The selective debromination was used also to prepare the alkaloid angelate esters germanitrine, cevadine, and escholerine. In the alkaloid series, sodium acetate was used to neutralize liberated hydrogen bromide. Triethylamine was not necessary to obtain a selective reduction, as apparently the alkaloid itself served as a suitable inhibitor of olefin saturation (Kupchan and Afonso, 1960). One might surmise that this reduction would not have been nearly so successful if chloro instead of bromo esters had been used.
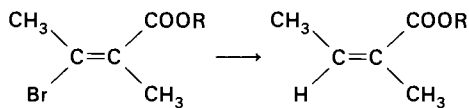
A similar selective bromine removal from a vinyl bromide was achieved, using conditions typical of a Rosenmund reduction. Hydrogen was passed

continuously through a mixture of 730 mg 3-bromo-A-nor-$\Delta^{3,5}$-cholesten-2-one (XXXVIII), 50 ml m-xylene, 0.1 ml quinoline–sulfur reagent, and 2.3 gm 6% palladium-on-barium sulfate while the mixture was stirred and refluxed. In 37 hours approximately 90% of the bromine had been removed, as determined by titration of the exhaust gas. A 73% yield of A-nor-$\Delta^{3,5}$-cholesten-2-one (XXXIX) was obtained, which could be reduced rapidly over platinum oxide in acetic acid to A-norcoprostan-2-one (XL). Hydrogenation of the bromo compound over platinum oxide was unsuccessful, presumably because the catalyst was poisoned by hydrogen bromide (Jacobs and Takahashi, 1958).

(XXXVIII)   (XXXIX)   (XL)
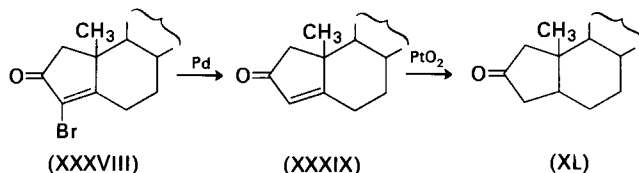
V. SELECTIVE HYDROGENATION OF POLYHALO COMPOUNDS

The preferred course of selective reduction of polyhalo compounds may to some extent be predicted. Halogens in positions allowing ready adsorption on the catalyst might be expected to be removed preferentially to halogens in hindered positions, and labile halogens, such as allylic or benzylic halogens, will be reduced in preference to less labile ones. Other structural features of the substrate may cause exceptions to these generalities. For instance, aromatization and selective dehalogenation of the adducts of dienes and chloroanil (XLI) occurred over palladium-on-carbon or platinum oxide. The latter catalyst also effected saturation of the isolated double bond (Gaertner, 1954). The chlorines lost were those least accessible to the catalyst, but were eliminated nonetheless during the aromatization process.

(XLI)
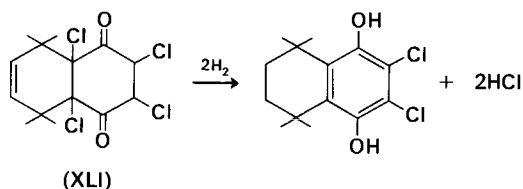
Hydrogenation of 2-methyl-3-(β-chloroethyl)-4,6-dichloropyridine (XLII) provides a good example of the different susceptibilities to dehalogenation of aromatic and aliphatic halogens in the same molecule. Reduction of 41 gm XLII in 2000 ml methanol over 30 gm palladium-on-barium sulfate ceased spontaneously when two equivalents of hydrogen had been absorbed

to afford XLIII. The authors commented that this result was somewhat surprising, as the β-chloroethyl group was expected to be the most readily attacked (Wilson and Harris, 1951). In general, aromatic halogen is reduced more easily than aliphatic halogen in neutral solution.
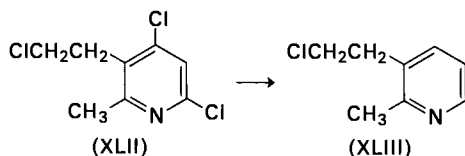
Dehalogenation of hexachlorocyclopentadiene (XLIV) over platinum oxide in methanol provides an illustration of the preferential hydrogenation of allylic chlorine in the presence of vinylic chlorine and tetrasubstituted carbon–carbon double bonds. Hydrogenation of XLIV proceeded stepwise, giving first XLV and then XLVI (McBee and Smith, 1955). Hydrogenation of 5,5-difluorotetrachlorocyclopentadiene (XLVII) occurred slowly and not so cleanly as hydrogenation of XLIV; both allylic fluorine and vinylic chlorine were removed. The decreased selectively obtained with XLVII was attributed to the greater stability of the carbon–fluorine linkage (McBee et al., 1955). Hydrogenation of XLIV over 5% palladium-on-carbon at 30–40°C afforded the dimer (XLVIII) in 30% yield (Rucker, 1959). The formation of the coupled product might be expected to be enhanced when palladium is used as the catalyst (Busch et al., 1936).
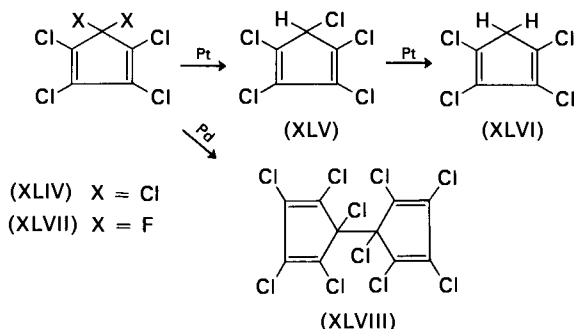
1. Polyhalogenated Benzenes

Early work on hydrogenation of polyhalogenated benzenes indicated that the fewer the remaining halogens, the more easily the reduction proceeds (Sabatier and Mailhe, 1904). Nonetheless under appropriate conditions good yields of intermediate products may be obtained. Hydrogenation of hexafluorobenzene at 300°C over either palladium or platinum catalysts

afforded pentafluorobenzenes in good yield (Florin *et al.*, 1959). Hydrogenation of 1.9 moles of 1,2,3-trichlorobenzene over 1.7 gm 5% palladium-on-carbon at 175°C afforded, after absoiption of 0.9 mole of hydrogen, a mixture of 1.1 moles of unchanged starting material, 0.1 mole of monochlorobenzene, and 0.7 mole of dichlorobenzene consisting of 95.4% *ortho* and 4.6% *meta* isomer. A similar hydrogenation of 1.8 moles of 1,2,3,4-tetrachlorobenzene afforded 1.0 mole of unchanged starting material and 0.7 mole of trichlorobenzene containing 98.4% of the 1,2,3- and 1.6% of the 1,2,4-isomer. Hydrogenations of this type may also be carried out continuously by maintaining the reaction mixtures under partial reflux and removing the lower-boiling products as they are formed (Redman and Weimer, 1960).

2. Compounds with Different Halogens

The ease of removal of halogen by catalytic dehalogenation might be expected to be related inversely to the carbon–halogen bond strength and to increase in the order, fluorine < chlorine < bromine < iodine. Considerable evidence indicates this is so, and the generality is probably a safe one to follow in predicting the loss of one halogen over another in competitive hydrogenations (Vavon and Mathieu, 1938). In noncompetitive hydrogenations the rates of reduction need not follow this order; dehydrohalogenation of a series of chloro- and bromo-5-alkylbarbituric acids over colloidal platinum in aqueous alcohol proceeded in the case of the isopropyl and isoamyl derivatives about 4 times more rapidly with the chloro compounds (Hughes and Macbeth, 1938). These results may be attributed to, among other things, different levels of catalyst deactivation or activation by the two halogen acids.

The lability of chlorine relative to fluorine is illustrated by the selective dechlorination of chlorotetrafluorobenzene and 2-chloroheptafluorotoluene over palladium-on-carbon at 280°C (Florin *et al.*, 1959).* Only about 1% of fluorine was removed in the reductions.
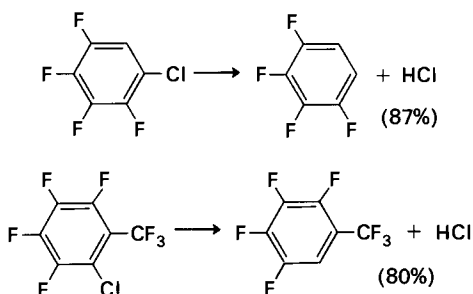
* Vapor phase dehydrohalogenations are rare, but can apparently be quite successful (Howk, 1963).

In a further example, the chlorine atoms of 1,1-difluoro-2,2-dichloro-3-phenylcyclobutene (XLIX) were removed preferentially by hydrogenation over 7% palladium-on-carbon in methanol containing sodium carbonate, to afford the saturated difluoro compound (L) in 36% yield; hydrolysis in concentrated sulfuric acid at 100°C preferentially removed the fluorines (Roberts et al., 1953). The yield of difluoro compound (L) was subsequently raised to 78–85% by using sodium acetate as a buffer in place of sodium carbonate in the hydrogenation (Manatt et al., 1964):

(XLIX)   (L)
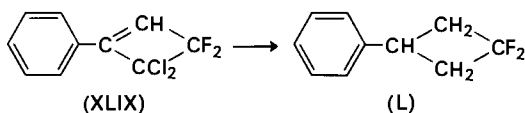
The buffer also had a marked effect in the selective dehydrohalogenation of 5-bromo-5-fluoro-6-hydroxyhydrouracil (LI) over 10% palladium-on-carbon in water. With sodium acetate present, 80% 5-fluoro-6-hydroxyhydrouracil (LII) and 20% 5-fluorouracil (LIII) were obtained, without it only 5-fluorouracil (Lozeron et al., 1964). The authors advanced an explanation for these different results. They assumed that the initial addition of hypobromous acid to fluorouracil followed the usual *trans* course. Hydrogenation of LI without sodium acetate was assumed to proceed without inversion to afford *cis*-LII, which was readily dehydrated to LIII, whereas in the buffered solution hydrogenation was assumed to proceed with 80% inversion to afford *trans*-LII, which was shown to be stable to dehydration in acidic media.

(LIII)   (LI)   (LII)
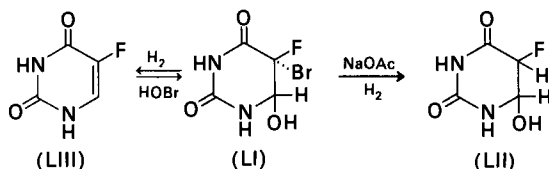
Bromine may be selectively removed by hydrogenation in molecules containing both chlorine and bromine, illustrated by the following two examples. Bromine was selectively removed from 4-acetamino-2-bromo-5-(2,4-dichlorophenyl)thiazole by 10% palladium-on-carbon in ethanol containing potassium hydroxide. Despite the presence of divalent sulfur, the reduction proceeded at a moderate rate; with a 15% catalyst loading level the reduction was complete in 2 hours (Johnson and Nasutavicus, 1963).
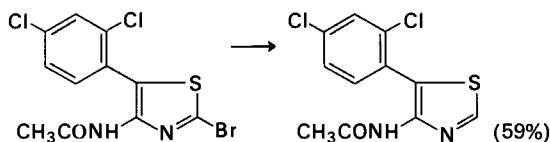
Chlorobromophenols were selectively reduced to the corresponding chlorophenols over palladium catalysts. For instance, 4-bromo-2,6-dichlorophenol, in a mixture of benzene and cyclohexane containing sodium acetate, was reduced over palladium at 27–44°C and 41–77 psig until one mole equivalent of hydrogen was absorbed. The yield of 2,6-dichlorophenol, after distillation, was 85.8 % (Britton and Keil, 1955).
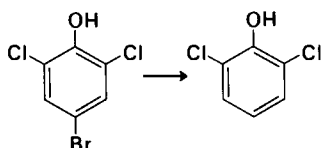
3. Several Halogens Attached to a Single Carbon

An accumulation of halogen on a single carbon atom increases the ease of dehalogenation, as evidenced by the selective hydrogenation of hexachlorocyclopentadiene (XLIV) and the following examples. Even the very stable carbon–fluorine bond is activated toward dehalogenation by the presence of an additional fluorine (Fuqua *et al.*, 1964).
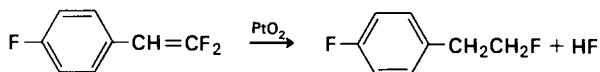
The increasing stability to hydrogenation of the intermediate products facilitates successive removal of halogens, and conditions may usually be found for selective stepwise hydrogenation. Selective dehalogenation of the dihalo compound 3,3-dichloro-2-oxohexamethyleneimine (LIV) afforded the monochloro derivative (LV) in excellent yield:

(LIV)   (LV)
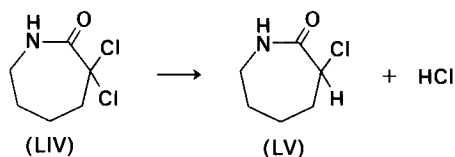
The reduction, carried out over 5 % palladium-on-carbon in acetic acid containing two moles of sodium acetate per mole of substrate, gave the monochloro derivative in 88 % yield. Instead of sodium acetate, an excess of pyridine or an excess of alcoholic ammonia may be used. The use of anhydrous ammonia at 20 atm pressure was unsatisfactory. The corresponding dibromo compound was similarly reduced to the monobromo derivative in 98 % yield (Wineman *et al.*, 1958).

Similarly, a stepwise catalytic reduction of 6-trichloromethylpurine (LVI) was achieved over 5 % platinum-on-carbon. Reduction of 2.4 gm LVI in 100 ml ethanol over 100 mg catalyst afforded 6-dichloromethylpurine (LVII) in 75 % yield, after absorption of one equivalent of hydrogen. If the

reduction were continued, a troublesome mixture resulted. However, reduction of 4.8 gm LVI in 50 ml methanol containing 20 gm sodium acetate trihydrate over 480 mg catalyst afforded 6-chloromethylpurine (LVIIa) in 45% yield. Similar catalytic reductions of 6-tribromomethylpurine in the presence of sodium acetate afforded successively 6-dibromomethylpurine (58%) and 6-bromomethylpurine* (22%) (Cohen et al., 1962).

| (LVIIa) | (LVI) | (LVII) |
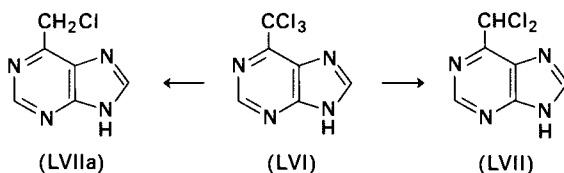
A fair yield (51%) of 3-bromocyclopropane-cis-1,2-diacetic acid (LIX) was obtained by hydrogenation of the 3,3-dibromo compound (LVIII), even though apparently no attempt was made to limit the hydrogen absorption. A mixture of 3.2 gm LVIII, 0.2 gm platinum oxide, 300 ml methanol, and 4 gm potassium hydroxide absorbed 1.4 equivalents of hydrogen in 24 hours. Similar results were obtained when the reduction was carried out over palladium-on-carbon or palladium-on-barium sulfate. Under the conditions of the reduction no hydrogenolysis of the cyclopropane ring occurred (Hofmann et al., 1959).

| (LVIII) | (LIX) |
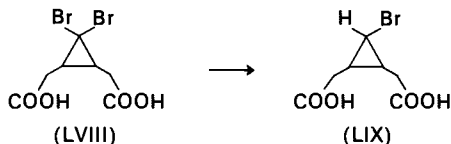
The depth of dehalogenation may also be affected by the solvent. Reduction of trichloroacetic acid or its esters over palladium-on-carbon in absolute ethanol ceased shortly after loss of one mole of halogen but, in aqueous ethanol, monochloroacetic acid was formed. Hydrogenation of ethyl dichloroacetate was shown to be suppressed by excess hydrogen chloride, which may account for the formation of this compound from ethyl trichloroacetate in anhydrous media (Baltzly and Phillips, 1946).

$$ClCH_2COOC_2H_5 \xleftarrow[H_2O]{EtOH} Cl_3CCOOC_2H_5 \xrightarrow{EtOH} Cl_2CHCOOC_2H_5$$
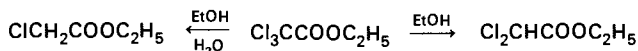
VI. REARRANGEMENTS

Rearrangement rarely accompanies catalytic dehalogenation, but a few well-characterized examples have been reported (Kwart and Null, 1958).

* A mixed catalyst, consisting of 10% platinum oxide and 9% palladium-on-calcium carbonate, is said to be particularly useful for dehalogenation of tribromo compounds (Marrian and Evans, 1964).

The bromo acids LX and LXII on reduction over 10% palladium-on-carbon in dilute methanolic potassium hydroxide at 40 psig afforded LXI and LXIII in good yield. (See, however, Boehme, 1958, 1959, Kwart and Null, 1959.)
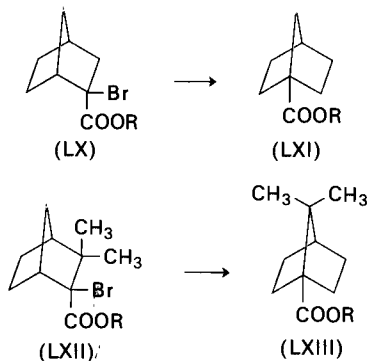
VII. COUPLING REACTIONS

Under certain conditions dehydrohalogenations follow an unusual course. Halogen is eliminated and a new carbon–carbon bond is formed (see also page 424). For instance, chlorobenzene, bromobenzene, and iodobenzene reduced by hydrogen in alkaline methanol over palladium-on-calcium carbonate gave 7%, 20%, and 56% yields of biphenyl, respectively. The results with hydrazine as a reducing agent were similar. Various p-substituted halobenzenes gave the corresponding biphenyls. Benzyl halides afforded considerable amounts of bibenzyls (Busch and Schmidt, 1929). Other platinum metals and nickel were ineffective in this type of reduction (Busch et al., 1936).

In a further investigation of this coupling reaction, Mayo and Hurwitz (1949) used methanol as both a solvent and reducing agent. With bromo-benzene as a model substrate, conditions of the reduction were systematically varied. A reduced palladium-on-calcium carbonate catalyst was found to be more active for halide removal than an unreduced catalyst, but the reduced catalyst gave less biphenyl. The yield of biphenyl also decreased with each reuse of the catalyst. The addition of water up to a concentration of 50% (by volume) increased the yield of biphenyl. To obtain the maximum yield of biphenyl, at least one equivalent of potassium hydroxide per mole of bromobenzene was required. With sodium methoxide, no reduction was observed in 24 hours. When hydrogen gas was bubbled through the reaction mixture, the rate of reduction was accelerated but the yield of biphenyl was sharply diminished. In this system, methanol seems to be specific for the pro-duction of biphenyl; with ethanol, isopropyl alcohol, and dioxane instead of methanol, reduction was negligible and only tars were formed. Mayo and Hurwitz concluded that the above and other evidence is consistent with the

view that the reduction of bromobenzene to biphenyl is a surface reaction, probably proceeding through adsorbed phenyl radicals.

VIII. DEHALOGENATION WITH HYDRAZINE

Hydrazine has been used as a source of hydrogen in dehalogenations, sometimes with excellent results. Dehalogenation of 3,5-dichloro-2-hydroxy-6-methylacetophenone over palladium-on-carbon in refluxing Methyl Cellosolve containing hydrazine gave after 48 hours the corresponding dechlorohydrazone (Cremer and Tarbell, 1961).
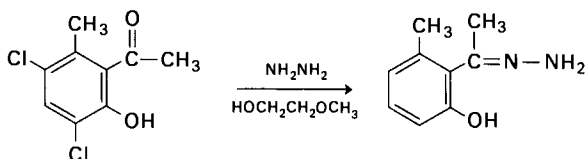
A dichlorobenzofuran (LXIV) was dehydrochlorinated in 94% yield by hydrazine and 5% palladium-on-carbon in refluxing Methyl Cellosolve (Chapman et al., 1960):
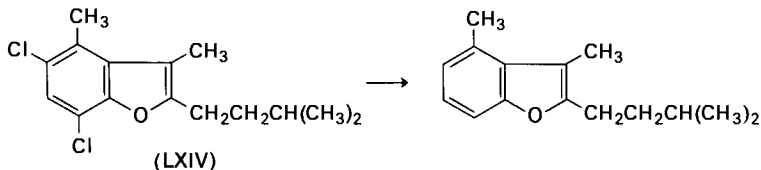
The same technique when applied to 9-bromo-3-nitrophenanthrene gave the debrominated amine in 87% yield (Mosby, 1959a):
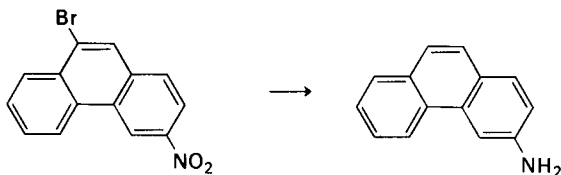
In a similar manner, 9-phenanthrylamine was formed in 91% yield from 9-bromo-10-nitrophenanthrene. This method of dehydrohalogenation was applied by Mosby to a number of haloaromatic compounds with, in general, excellent results (Mosby, 1959b). The subjects of dehydrohalogenation with hydrazine, as well as catalytic hydrazine reductions in general, have been comprehensively reviewed (Furst et al., 1965).

REFERENCES

Arkley, V., Gregory, G. I., and Walker, T., *J. Chem. Soc.* p. 1603 (1963).
Baltzly, R., and Phillips, A. P., *J. Am. Chem. Soc.* **68**, 261 (1946).

Barnes, R. A., and Gerber, N. N., *J. Org. Chem.* **26**, 4540 (1961).

Bavley, A., Gollaher, M. G., and McLamore, W. M., U.S. Patent 2,745,838, May 15, 1956.

Bendich, A., Russell, P. J., Jr., and Fox, J. J., *J. Am. Chem. Soc.* **76**, 6073 (1954).

Benington, F., Morin, R. D., and Clark, L. C., Jr., *J. Org. Chem.* **25**, 1542 (1690).

Bergman, E., *J. Org. Chem.* **28**, 2210 (1963).

Berkowitz, L., and Rylander, P. N., Unpublished observations, Engelhard Ind., 1958.

Blicke, F. F., and McCarty, F. J., *J. Org. Chem.* **24**, 1061 (1959).

Bobbitt, J. M., and Doolittle, R. E., *J. Org. Chem.* **29**, 2298 (1964).

Bobbitt, J. M., and Scola, D. A., *J. Org. Chem.* **25**, 560 (1960).

Boehme, W. R., *J. Am. Chem. Soc.* **80**, 4740 (1958).

Boehme, W. R., *J. Am. Chem. Soc.* **81**, 2762 (1959).

Britton, E. C., and Keil, T. R., U.S. Patent 2,725,402, Nov. 29, 1955.

Busch, M., and Schmidt, W., *Chem. Ber.* **62B**, 2612 (1929).

Busch, M., and Stöve, H., *Chem. Ber.* **49**, 1063 (1916).

Busch, M., Weber, W., Darboven, C., Renner, W., Hahn, H. J., Mathauser, G., Strätz, F., Zitzmann, K., and Engelhardt, H., *J. Prakt. Chem.* **146**, 1 (1936).

Carbon, J. A., *J. Am. Chem. Soc.* **80**, 6083 (1958).

Cava, M. P., and Napier, D. R., *J. Am. Chem. Soc.* **80**, 2255 (1958).

Chapman, D. D., Cremer, S. E., Carman, R. M., Kunstmann, M., McNally, J. G., Jr., Rosowsky, A., and Tarbell, D. S., *J. Am. Chem. Soc.* **82**, 1009 (1960).

Cohen, S., Thom, E., and Bendich, A., *J. Org. Chem.* **27**, 3545 (1962).

Conroy, H., *J. Am. Chem. Soc.* **77**, 5960 (1955).

Cope, A. C., and Gale, D. M., *J. Am. Chem. Soc.* **85**, 3743 (1963).

Corwin, A. H., and Kleinspehn, G. G., *J. Am. Chem. Soc.*, **75**, 2089 (1953).

Cremer, S. E., and Tarbell, D. S., *J. Org. Chem.* **26**, 3653 (1961).

Cristol, S. J., and Hause, N. L., *J. Am. Chem. Soc.* **74**, 2193 (1952).

Dietzler, A. J., and Keil, T. R., U.S. Patent 3,051,753, Aug. 28, 1962.

Dorfman, E., Weil, E. D., and Gruber, R. J., U.S. Patent 3,158,646, Nov. 24, 1964.

Florin, R. E., Pummer, W. J., and Wall, L. A., *J. Res. Natl. Bur. St.* **62**, 119 (1959).

Freedman, L. D., Doak, G. O., and Petit, E. L., *J. Am. Chem. Soc.* **77**, 4262 (1955).

Freifelder, M., Martin, W. B., Stone, G. R., and Coffin, E. L., *J. Org. Chem.* **26**, 383 (1961).

Fuqua, S. A., Parkhurst, R. M., and Silverstein, R. M., *Tetrahedron* **20**, 1625 (1964).

Furst, A., Berlo, R. C., and Hooton, S., *Chem. Rev.* **65**, 51 (1965).

Gaertner, R., *J. Am. Chem. Soc.* **76**, 6150 (1954).

Ham, G. E., and Coker, W. P., *J. Org. Chem.* **29**, 194 (1964).

Harris, S. A., and Folkers, K., *J. Am. Chem. Soc.* **61**, 1245 (1939).

Hasbrouck, L., Unpublished observations, Engelhard Ind., 1966.

Hofmann, K., Orochena, S. F., Sax, S. M., and Jeffrey, G. A., *J. Am. Chem. Soc.* **81**, 992 (1959).

Howk, B. W., U.S. Patent 3,110,742, Nov. 12, 1963.

Huffman, J. W., *J. Org. Chem.* **24**, 1759 (1959).

Hughes, G. K., and Macbeth, A. K., *J. Chem. Soc.* p. 1622 (1938).

Isogai, K., *Nippon Kagaku Zasshi* **81**, 1594 (1960).

Jacobs, T. L., and Takahashi, N., *J. Am. Chem. Soc.* **80**, 4865 (1958).

Johnson, F., and Nasutavicus, W. A., *J. Org. Chem.* **28**, 1877 (1963).

Kindler, K., Oelschläger, H., and Henrich, P., *Chem. Ber.* **86**, 501 (1953).

Kleinspehn, G. G., and Corwin, A. H., *J. Am. Chem. Soc.* **75**, 5295 (1953).

Kosak, J. R., U.S. Patent 3,145,231, Aug. 18, 1964.

Kupchan, S. M., and Afonso, A., *J. Org. Chem.* **25**, 2217 (1960).

Kwart, H., and Null, G., *J. Am. Chem. Soc.* **80**, 248 (1958).

Kwart, H., and Null, G., *J. Am. Chem. Soc.* **81**, 2765 (1959).

Lozeron, H. A., Gordon, M. P., Gabriel, T., Tautz, W., and Duschinsky, R., *Biochemistry* 3 1844 (1964).
Lutz, R. E., Ashburn, G., and Rowlett, R. J., Jr., *J. Am. Chem. Soc.* **68**, 1322 (1946).
McBee, E. T., and Smith, D. K., *J. Am. Chem. Soc.* **77**, 389 (1955).
McBee, E. T., Smith, D. K., and Ungnade, H. E., *J. Am. Chem. Soc.* **77**, 387 (1955).
McMullen, E. J., Henze, H. R., and Wyatt, B. W., *J. Am. Chem. Soc.* **76**, 5636 (1954).
Magerlein, B. J., and Kagan, F., *J. Am. Chem. Soc.* **82**, 593 (1960).
Manatt, S. L., Vogel, M., Knutson, D., and Roberts, J. D., *J. Am. Chem. Soc.* **86**, 2645 (1964).
Marrian, D. H., and Evans, E. A., U.S. Patent 3,157,684, Nov. 17, 1964.
Marshall, J. R., and Walker, J., *J. Chem. Soc.* p. 1004 (1951).
Mayo, F. R., and Hurwitz, M. D., *J. Am. Chem. Soc.* **71**, 776 (1949).
Meschke, R. W., and Hartung, W. H., *J. Org. Chem.* **25**, 137 (1960).
Michelson, A. M., and Todd, A. R., *J. Chem. Soc.* p. 816 (1955).
Mizzoni, R. H., and Spoerri, P. E., *J. Am. Chem. Soc.* **73**, 1873 (1951).
Mladenovic, M., *Bull. Soc. Chim. Roy. Yougoslav.* **4**, 187 (1933).
Mosby, W. L., *J. Org. Chem.* **24**, 421 (1959a).
Mosby, W. L., *Chem. Ind.* (*London*) p. 1348 (1959b).
Nickon, A., *J. Am. Chem. Soc.* **77**, 4094 (1955).
Overberger, C. G., and Kogon, I. C., *J. Am. Chem. Soc.* **76**, 1879 (1954).
Overberger, C. G., and Monagle, J. J., *J. Am. Chem. Soc.* **78**, 4470 (1956).
Pfitzner, K. E., and Moffatt, J. G., *J. Org. Chem.* **29**, 1508 (1964).
Pickard, P. L., and Lochte, H. L., *J. Am. Chem. Soc.* **69**, 14 (1947).
Redman, H. E., and Weimer, P. E., U.S. Patent 2,943,114, June 28, 1960.
Reinecke, M. G., *J. Org. Chem.* **29**, 299 (1964).
Roberts, J. D., Kline, G. B., and Simmons, H. E., Jr., *J. Am. Chem. Soc.* **75**, 4765 (1953).
Ross, L. O., Goodman, L., and Baker, B. R., *J. Am. Chem. Soc.* **81**, 3108 (1959).
Rucker, J. T., U.S. Patent 2,908,723, Oct. 13, 1959.
Rylander, P. N., Kilroy, M., and Coven, V., *Engelhard Ind. Tech. Bull.* **6**, 11 (1965).
Sabatier, P., and Mailhe, A., *Compt. Rend.* **138**, 245 (1904).
Sargent, L. J., and Agar, J. H., *J. Org. Chem.* **23**, 1938 (1958).
Schulenberg, J. W., and Archer, S., *J. Org. Chem.* **30**, 1279 (1965).
Skita, A., and Meyer, W. A., *Chem. Ber.* **45**, 3579 (1912).
Southwick A., Unpublished observations, Engelhard Ind., 1962.
Sperber, N., Sherlock, M., Papa, D., and Kender, D., *J. Am. Chem. Soc.* **81**, 704 (1959).
Spiegler, L., U.S. Patent 3,073,865, Jan. 15, 1963.
Stephenson, E. F. M., *J. Chem. Soc.* p. 1913 (1963).
Swarts, F., *Bull. Sci. Acad. Roy. Belg.* **22**, 122 (1936).
Taub, D., Hoffsommer, R. D., Slates, H. L., and Wendler, N. L., *J. Org. Chem.* **26**, 2852 (1961).
Vavon, G., and Mathieu, R., *Compt. Rend.* **206**, 1387 (1938).
Whittaker, N., *J. Chem. Soc.* p. 1565 (1950).
Whittaker, N., *J. Chem. Soc.* p. 1646 (1953).
Wilson, A. N., and Harris, S. A., *J. Am. Chem. Soc.,* **73**, 2388 (1951).
Wineman, R. J., Hsu, E.-P. T., and Anagnostopoulos, C. E., *J. Am. Chem. Soc.* **80**, 6233 (1958).
Woodward, R. B., *J. Am. Chem. Soc.* **62**, 1208 (1940).

25

Miscellaneous Hydrogenolyses

Catalytic hydrogenolysis, defined as the cleavage of a molecule into fragments by hydrogen in the presence of a catalyst, has proved to be a most useful process in synthetic and degradative chemistry. Some hydrogenolysis reactions have acquired special names, e.g., dehydrohalogenation and debenzylation. Others fit no general category and their classification poses a problem. In this chapter hydrogenolyses are grouped according to the type of bond undergoing cleavage.

I. ALLYLIC OXYGEN $\underset{/}{\overset{\backslash}{C}}=\overset{|}{C}-\overset{|}{C}-O-$

Compounds containing an allylic oxygen function are numerous and many have been subjected to hydrogenation. The course of hydrogenation has varied from complete hydrogenolysis of the oxygen function to its complete retention, but it is difficult to predict, except in the most general way, what course the reduction will follow. Allylic oxygen undergoes hydrogenolysis of the carbon–oxygen bond much more readily than the corresponding saturated structure; often the saturated molecule appears to be completely stable under the same conditions that permitted facile hydrogenolysis of the allylic function. But since the olefinic linkage is itself readily hydrogenated the outcome of reduction is determined by the relative rates of the competing reactions.
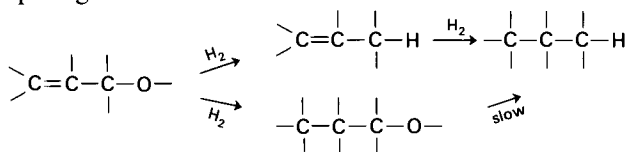
Compounds with bulky substituents in the neighborhood of the double bond (Wiberg and Hutton, 1954; Adams and Gianturco, 1956), or compounds with tetrasubstituted double bonds (Boekelheide and Chang, 1964; Godfrey

et al., 1955; Stedman *et al.*, 1964), might be expected to and do undergo extensive hydrogenolysis, inasmuch as the olefinic function is relatively inaccessible to approach by the catalyst. On the other hand, extensive hydrogenolysis also occurred during hydrogenation of I over platinum oxide in methanol (Meinwald *et al.*, 1958), and of II over platinum oxide in acetic acid (Meinwald and Frauenglass, 1960) or ethanol (Noland *et al.*, 1959). Each of these compounds would seem to have an unhindered olefinic bond, allowing its facile saturation. Reduction of III over platinum oxide in ethanol afforded, however, mainly the saturated lactone, and only 11 % of the hydrogenolysis product cyclohexylacetic acid (Newman and VanderWerf, 1945). These results are not consistent with the generality that disubstituted olefins are reduced more easily than trisubstituted olefins.

(I)   (II)   (III)
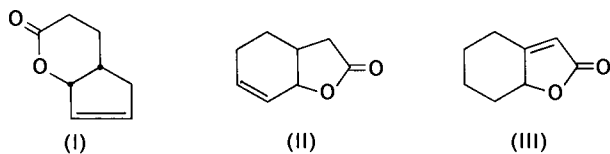
The extent of hydrogenolysis may be influenced decisively by structural changes remote from the allylic system. The exocyclic double bond of the azlactone (IV) was reduced over palladium-on-carbon in dioxane with little or no hydrogenolysis of the allylic acetate groups, whereas, in marked contrast, the substituted acrylic acids and esters (V) underwent only hydrogenolysis (Galantay *et al.*, 1963).

(IV)

(V)
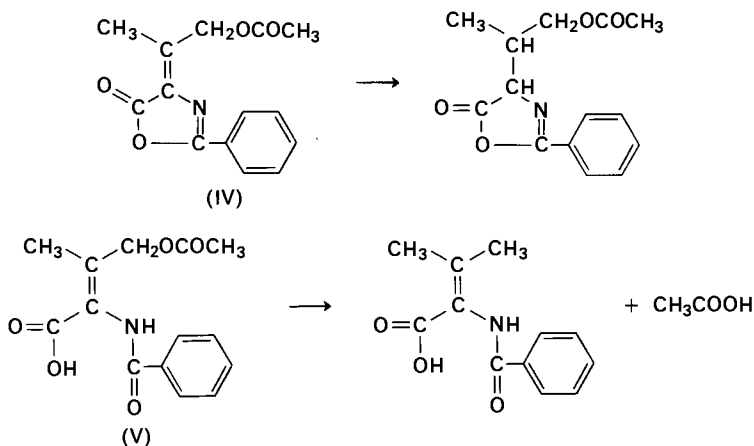
A. SOLVENT

The solvent may have an important influence on the products of reduction of allylic oxygen compounds. Hydrogenolysis of cinnamyl alcohol over 5 %

palladium-on-carbon varied markedly with the solvent, increasing with polarity and acidity, as shown in Table I (Rylander and Himelstein, 1964a). A similar trend was found in hydrogenation of cinnamyl alcohol over platinum oxide and palladium oxide; hydrogenolysis increased with solvent

TABLE I

HYDROGENOLYSIS OF CINNAMYL ALCOHOL IN VARIOUS SOLVENTS[a]

Solvent	Rate (ml H_2/minute)	Percent hydrogenolysis
Methanol	70	0
Methanol (50% aq).	—	11
Acetic acid	50	25
Methanol (+ 2% conc. HCl)	80	53

[a] Each experiment was carried out with 200 mg 5% palladium-on-carbon at room temperature and pressure. In separate experiments, the catalyst loading was varied from 100 to 1000 mg, but only the rate was changed; the extent of hydrogenolysis was independent of the amount of catalyst.

in the order, ethanol, acetic acid, ethanol–hydrochloric acid, acetic acid–hydrochloric acid (Nishimura et al., 1960). Acidic media promoted hydrogenolysis of VI over rhodium-on-alumina. In water the product was about 50% each of VII and VIII; in 5% acetic acid much less VII was formed, and in 50% acetic virtually none (Cline et al., 1959).
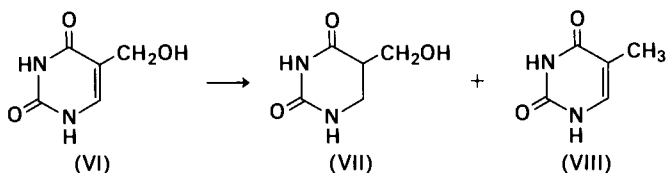
Weak acids do not always increase hydrogenolysis; the presence of acetic acid in ethyl acetate appreciably decreased hydrogenolysis of the oxygen function during reduction of 3-hydroxy-, 3-methoxy-, and 3-acetoxy-Δ^4-steroids over platinum oxide. On the other hand, hydrogenolysis was markedly increased by small amounts of sulfuric acid or perchloric acid (Shoppee et al., 1957). Hydrogenation of the allylic alcohol (IX) as the hydrochloride in ethanol over palladium-on-carbon afforded the cyclic
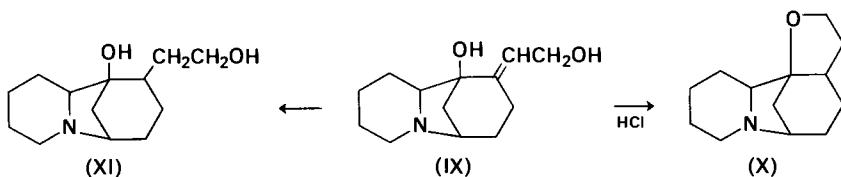
ether (X), whereas in neutral solution the diol (XI) was formed. Apparently acid promoted formation of an intermediate unsaturated cyclic ether by displacement on the allylic alcohol (Nakano *et al.*, 1963).

The extent of hydrogenolysis is at times markedly dependent on the polarity of the solvent. Reduction of dehydrogriseofulvin (XII) in relatively nonpolar ethyl acetate with a high catalyst loading (2 parts catalyst, 1 part substrate) gave, after absorption of 0.9 mole of hydrogen, 5–10% unchanged (XII), 55–60% griseofulvin (XIII), 10–15% dihydrogriseofulvin (XIV), and about 20% of a hydrogenolysis product, the benzophenone (XV). In dioxane and 1,2-dimethoxyethane hydrogenolysis amounted to 40–50%, and in ethanol 90%. Maximum yields of XIII were obtained with a catalyst-to-substrate ratio of 2:1. Ratios of 1:1 and 1:2 gave much slower hydro-genations and increasingly larger amount of XIV and XV. Hydrogenation of optically active XII gave (+)-XIII as the major product and some (+)-XIV. Hydrogenation of XII proceeded exclusively from one side of the molecule, the side adjacent to the ether oxygen. The authors commented that an in-spection of a model of XII provides insufficient reason to expect such a high degree of stereoselectivity from steric factors alone. They suggested, following others, that possible orbital overlap of the π electrons of the carbonyl with those of the dienone system may play a decisive role (Taub *et al.*, 1963).

(XII)   (XIII)   (XIV)

(XV)
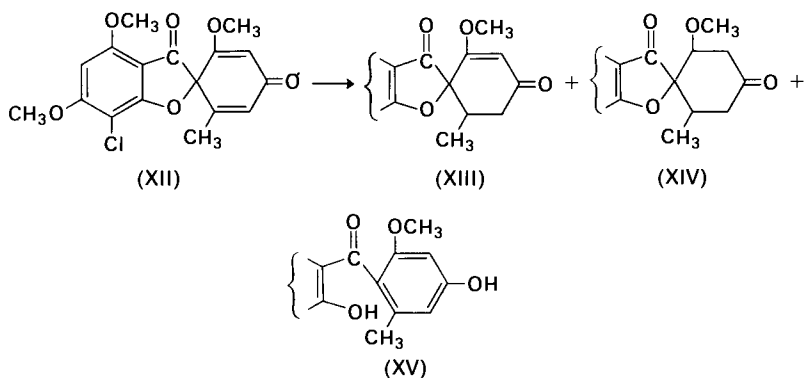
B. Catalysts

Few comparisons have been made of the effect of different platinum metals on the products of reduction of an allylic oxygen compound. Com-parisons are complicated by the effect of trace quantities of acid in the catalyst, which may drastically alter the results. Little or no hydrogenolysis occurred during hydrogenation of cinnamyl alcohol over 5% palladium-, 5% platinum-, or 5% rhodium-on-carbon in ethanol (Rylander and Himelstein, 1964b), whereas over palladium chloride-on-carbon (Hartung, 1928) the

product was a mixture of about equal amounts of hydrocinnamyl alcohol and propylbenzene (Baltzly and Buck, 1943).

Products obtained by hydrogenation over platinum oxide may vary drastically with the source of the catalyst. The yields of hydrocarbon obtained on reduction of cholest-4-en-3β-ol over platinum oxide varied from 1% to 73%, depending on how the catalyst was prepared. Hydrogenolysis was inhibited by small quantities of sodium salts remaining in the virgin catalyst or by addition of small amounts of sodium nitrite, cyanide, or hydroxide to a used catalyst. Extensive hydrogenolysis occurred if the platinum oxide were prereduced and washed with water to remove the sodium salts. The yield of cholestanol remained relatively constant regardless of the catalyst, whereas the yield of coprostanol varied over a wide range, inversely with the yield of hydrocarbon. The yields of coprostanol depended on the ratio of hexachloroplatinic acid to sodium nitrate used in preparation of the catalyst. When the ratio of platinum salt to sodium nitrate was 1:10, the yield of coprostanol was 8–10%; with a ratio of 1:20, the yield of coprostanol was 67–71% (Dart and Henbest, 1960).

The products obtained on reduction of rotenone (XVI) over platinum oxide were different for fresh and reused catalyst. Rotenonic acid, formed through cleavage of the furan ring as indicated, was the major product when freshly prepared platinum oxide in neutral solution was used. If the same catalyst were used a second time, dihydrorotenone predominated. Addition of a small amount of pyridine to hydrogenations over a reused catalyst did not increase the yield of rotenonic acid, but hydrogenation of rotenone over a palladium-on-barium sulfate catalyst in pyridine solution gave a quantitative yield of rotenonic acid (Haller and Schaffer, 1933).

(XVI)
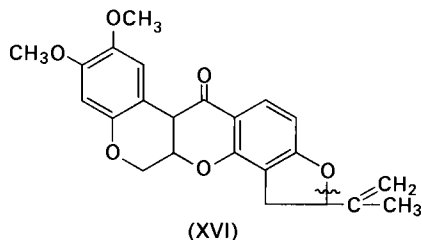
An impressive difference between platinum oxide and 19% palladium-on-carbon, on the one hand, and Raney nickel, on the other, has been observed in hydrogenolysis of 7-methylcholest-5-ene-3β,7β-diol (XVII). Over the platinum metal catalysts in acetic acid the allylic hydroxyl is readily lost, whereas the substrate is almost inert to Raney nickel even at 80°C and 1500 psig. The authors (Callow and Thompson, 1964) suggested that attack occurs at the α-face of the molecule and that hydrogenolysis of the carbon–oxygen bond over the platinum metals occurs with inversion by an S_N2

mechanism. Nickel normally effects hydrogenolysis without inversion, and hence would be inactive if presented the α-face of the molecule (Mitsui *et al.*, 1963).

(XVII)
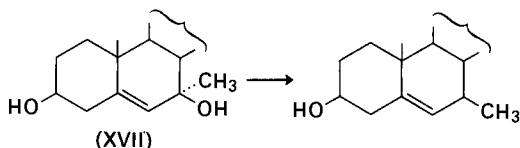
Allylic alcohols contained in long-chain molecules seem to be particularly susceptible to hydrogenolysis (Heilbron and Thompson, 1929; Rowland *et al.*, 1956; Smith *et al.*, 1960). Zajcew (1958) has developed a palladium-on-carbon catalyst modified by silver and bismuth* for use in reduction of this type of compound when hydrogenolysis is to be avoided. Castor oil was reduced over this modified catalyst with very little hydrogenolysis, whereas over an unmodified palladium-on-carbon catalyst loss of hydroxyl was extensive. This palladium-silver-bismuth catalyst might also prove useful in reduction of other types of allylic oxygen compound, but apparently has not yet been tested.

C. DOUBLE-BOND MIGRATION

Hydrogenolysis of the carbon–oxygen bond may be accompanied by migration of the carbon–carbon double bond. Reduction of ψ-santonin (XVIII) over palladium in acetic acid afforded XIX, in which the double bond has migrated away from what would be expected to be the thermodynamically stable position. Dauben and Hance (1955) have pointed out that this type of migration may be masked in many hydrogenolyses, due to the fact that saturation of the double bond generally occurs. In the ψ-santonin series, it was found that under any hydrogenation conditions cleavage of the lactone occurred, but that the reaction would stop cleanly after absorption of one mole of hydrogen if palladium-on-strontium carbonate were the catalyst (Dauben *et al.*, 1960a).

(XVIII)   (XIX)
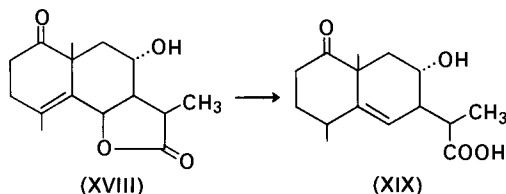
It has been suggested that hydrogenolysis is characteristic of an axial oxygen grouping (Dauben *et al.*, 1960b). The *trans*-(−)-α-santonin (with an equatorial oxygen) gave the tetrahydro derivative with the lactone intact,

* Manufactured by Engelhard Industries, Newark, N.J.
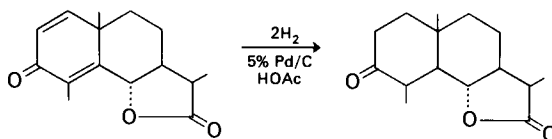
while the *cis* isomer, santonin-C (with an axial oxygen), underwent hydrogenolysis in addition to olefin saturation:
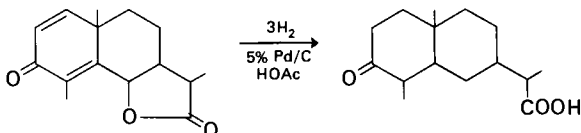
1. *Allylic Alcohols*

Hydrogenation of allyl alcohols may also be accompanied by double-bond migration affording aldehydes or ketones, which may or may not, depending on the catalyst, undergo further reduction. If the catalyst is not suitable for hydrogenation of the carbonyl, less than one mole of hydrogen may be absorbed (Mitsui and Saito, 1961). A measure of the relative effectiveness of catalysts in promoting isomerization of an unsaturated alcohol to a saturated ketone has been made, using cyclohexen-2-ol as a model substrate. Cyclohexen-2-ol was reduced in ethanol over 5% palladium-on-carbon, 5% platinum-on-carbon, and 5% rhodium-on-carbon until a sharp break in the hydrogenation rate occurred, indicating disappearance of the olefin either by saturation or by isomerization to the ketone (Table II). Palladium and rhodium caused appreciable isomerization, platinum none (Rylander and Himelstein, 1964b).

TABLE II

HYDROGENATION OF CYCLOHEXEN-2-OL[a]

Catalyst	Mole percent in product	
	Cyclohexanol	Cyclohexanone
5% Pd/C	67	33
5% Pt/C	100	0
5% Rh/C	66	34

[a] Each experiment was carried out with 200 mg prereduced catalyst, 10 ml 95% ethanol and 0.01 mole of cyclohexenol at room temperature, and interrupted when an abrupt decrease in rate occurred.

In another study (Goering *et al.*, 1961), the catalyst support (or perhaps metal concentration) was found to influence the extent of isomerization.

Hydrogenation of the axial allylic alcohol (XX) over 30% palladium-on-carbon in methanol resulted in roughly equal amounts of the saturated axial alcohol (XXI) and the saturated ketone (XXII). In contrast, hydrogenation of XX over 5% palladium-on-barium sulfate gave substantially pure XXI with only a trace of ketone. Hydrogenation of the equatorial isomer did not proceed as cleanly, and over either catalyst a mixture of ketone and saturated alcohol was formed. The saturated alcohol was not homogeneous and consisted of 70% of the equatorial alcohol and 30% of the axial alcohol. The mixture may have arisen by hydrogenation of the intermediate ketone.

(XX)   (XXI)   (XXII)
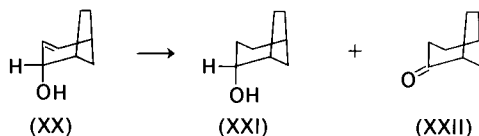
2. Allylic Rearrangement

Allylic alcohols may undergo a migration of the hydroxyl group during hydrogenation. About 10% of the rearranged product (XXIV) was obtained on reduction of the allylic alcohol (XXIII) over platinum oxide in ethanol containing pivalic acid. Evidently catalyst and hydrogen are necessary for the rearrangements, as XXIV was recovered unchanged after treatment with an ethanol solution of pivalic acid (Dart and Henbest, 1960).

(XXIII)   (XXIV)
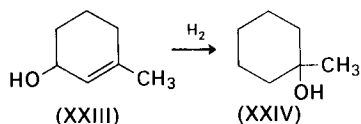
D. ALLYLIC OXYGEN AND NITROGEN COMPOUNDS

A number of compounds contain both oxygen and nitrogen substituents allylic to the same carbon–carbon double bond. Hydrogenation of these compounds seems to favor strongly preferential cleavage of the allylic carbon–oxygen bond (Boekelheide and Chang, 1964; Adams and Gianturco, 1956), unless the nitrogen atom is quaternary (Dickinson et al., 1964). Catalytic hydrogenation of the allylic amino lactone (XXV) over 10% palladium-on-carbon in ethanol afforded essentially pure 3-phenyl-4-piperidinobutyric acid (XXVI) (Jenny and Druey, 1960), by preferential cleavage of the carbon–oxygen bond:

(XXV)   (XXVI)
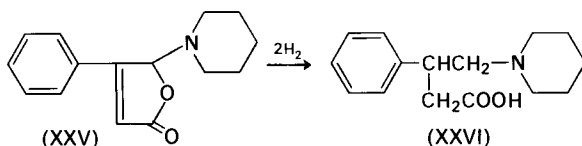
Because of the difference in ease of hydrogenolysis of the carbon–oxygen and carbon–nitrogen bonds, analogous oxygen and nitrogen compounds may afford completely different products on reduction. Reduction of the dienone–lactone (XXVII) over platinum oxide in ethanol gave the hydrogenolysis product, 4′-hydroxybiphenyl-2-carboxylic acid (XXVIII). The authors suggested that a concerted reduction, as shown, appears more probable than formation and reduction of a dienol. The corresponding N-ethyl lactam, on the other hand, did not suffer hydrogenolysis and aromatization so readily, and gave instead the corresponding tetrahydro derivative (Hey et al., 1963).

(XXVII)   (XXVIII)
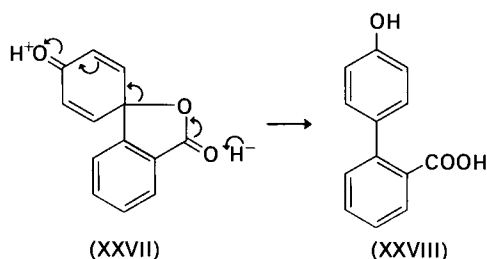
E. COUPLING REACTIONS

An unusual coupling reaction has been observed in hydrogenolysis of certain 7-substituted cycloheptatrienes over 5% palladium-on-carbon in ethyl acetate. Hydrogenolysis of cycloheptatrienyl acetate (XXIX) gave, after absorption of 3.25 equivalents of hydrogen, only dicycloheptyl (XXX):

(XXIX)   (XXX)
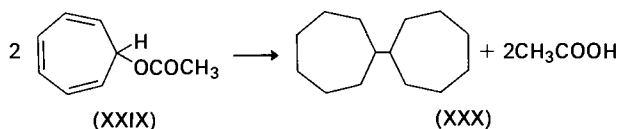
Ditropyl was found when the reduction was interrupted after 0.64 equivalent of hydrogen had been absorbed. The extent of dicycloheptyl formation, of hydrogenolysis to cycloheptane, and of simple double-bond saturation depends on the substituents. Only cycloheptatrienyl diethylamine gave appreciable amounts of the hydrogenolysis product, cycloheptane. Ether substituents favor reduction to the cycloheptyl ether. No coupling whatsoever occurred on reduction of the corresponding isomeric benzyl compounds. The authors pointed out that dimerization of tropyl radicals is favored by their symmetry; benzyl radicals could dimerize only in specific orientations. No products were detected that might have arisen by isomerization of tropyl radicals to benzyl radicals, a reaction estimated to be exothermic by 20 kcal/ mole in the gas phase (Orlando and Weiss, 1962).

II. ALLYLIC NITROGEN $\quad \underset{/}{\overset{\backslash}{C}}=\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{|}{N}-$

There are few examples of hydrogenation of relatively simple molecules containing an allylic nitrogen atom. Most examples are from the alkaloid field, where extensive secondary changes may also occur. Whether hydrogenation or hydrogenolysis will occur seems to depend here, as with allylic oxygen compounds, on rather subtle factors, and the major products are difficult to predict, lacking a close analogy. One gathers that substrate structure and solvent are of more importance than the catalyst in determining the course of reduction; no systematic study of the effect of catalyst has been made, however. The compounds XXXI and XXXII are similar, but their hydrogenations proceeded differently. Reduction of XXXI over platinum oxide in alcohol absorbed two moles of hydrogen at constant rate with complete cleavage of the allylic carbon–nitrogen bond, but XXXII under similar conditions absorbed only 1.52 moles of hydrogen and gave an approximately equimolar mixture of N-methylpiperidine methiodide and N,N-dimethylpentylamine hydriodide (Dickinson *et al.*, 1964). The authors suggested that, in the alkaloid case, the hydrogenation followed only one course because of the affinity of the indolic portion of the molecule for the catalyst. Alternatively, since hydrogenolysis undoubtedly precedes olefin saturation, the difference between the alkaloids and the pyridine may be a reflection of the relative ease of saturation of tri- and disubstituted olefins. Earlier workers observed no hydrogenolysis on reduction of XXXII over platinum oxide in alcohol (Renshaw and Conn, 1938). If the nitrogen atom of XXXI (R = OH) is not quaternary, the allylic oxygen bond and not the allylic nitrogen bond is cleaved (Olin, 1962).
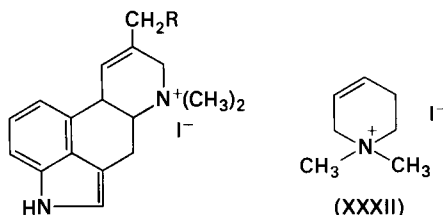
A. QUATERNARY ALLYLIC AMINES

Quaternary allylic amines undergo hydrogenolysis readily (Emde, 1932; Emde and Kull, 1935, 1936; Bartlett *et al.*, 1963). An interesting use was made of the reaction in the synthesis of the biologically important 6-methyl-3-alkoxy-3,5-diene steroids. Hydrogenation of the free allylic amine over 5%

palladium-on-carbon in methanol was not selective, and cleavage of the carbon–nitrogen bond and reduction of the 3,5-diene system occurred concomitantly. However, satisfactory yields of the 6-methyl enol ethers (XXXIV) were obtained if the reductions were carried out with the amine oxide hydrate (XXXIII) or with a quaternary salt, and were stopped after absorption of one equivalent of hydrogen. The quaternary salts were unstable, and high catalyst loadings were recommended to ensure a rapid hydrogenation. The yields were improved if one equivalent of sodium acetate were added to the reaction mixture. The most satisfactory way of carrying out the hydrogenolysis was by hydrogen transfer, using, for example, cyclohexene as a hydrogen donor and palladium-on-carbon catalyst. Only hydrogenolysis occurred and there was no reduction of other functions. The preferred substrate in the transfer reaction was the amine–borane adducts; the quaternary salts and N-oxide could not be used, as they were rapidly converted under the experimental conditions to the 6-methylene derivative (Burn et al., 1965).

(XXXIII)   (XXXIV)
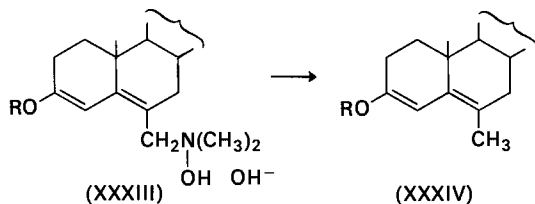
B. SOLVENT

Hydrogenations of allylic amines show marked solvent effects, analogous to those observed with allylic oxygen compounds, but perhaps accentuated with allylic amines because of the basicity of the nitrogen atom. Hydrogenation of demethoxy-β-erythroidine (XXXV) over platinum oxide in ethanol–hydrochloric acid can be made to yield stereospecifically di-, tetra-, and hexahydro derivatives, a fact that was of importance in elucidation of the structure. In neutral ethanol the reduction proceeded much more slowly and afforded a compound (XXXVI) with a considerably changed structure. The authors believed the change to occur through hydrogenolysis of the carbon–nitrogen bond, aromatization through isomerization, and finally 1,4-addition of the secondary amine to the conjugated lactone.

(XXXV)   (XXXVI)
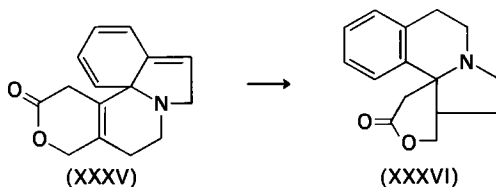
The nitrogen atom in XXXV is allylic to three aliphatic carbon–carbon double bonds, and would be expected to be particularly susceptible to hydrogenolysis.

Either the hydrogenation product (XXXVIII) or the hydrogenolysis product (XXXIX) could be obtained in reduction of XXXVII by proper choice of solvent. Reduction of XXXVII in acetic acid over platinum oxide gave XXXVIII, but reduction in ethanol of either the free amine or the hydrochloride over either platinum oxide or palladium-on-barium sulfate resulted in loss of the nitrogen moiety (Bailey and Lutz, 1945).
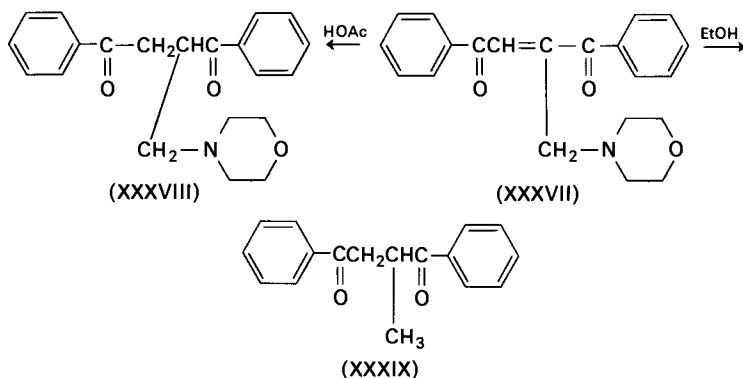
Hydrogenolysis of XL in 85% ethanol afforded thymine (XLI). The double bond remained intact (Burckhalter *et al.*, 1960). The olefinic linkage of vinylogous amides is reduced with more difficulty than isolated olefins.
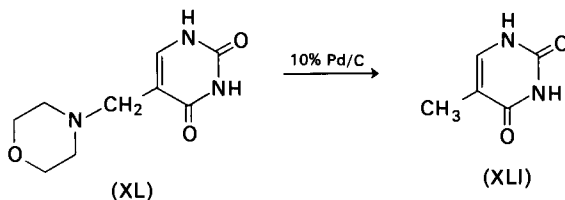
III. VINYL FUNCTIONS $\overset{\backslash}{\underset{/}{C}} = \underset{|}{C} - X -$ (X = O, N, etc.)

The outcome of catalytic reduction of vinyl compounds, as with allylic compounds, depends on the relative rates of the hydrogenation and hydrogenolysis reactions:
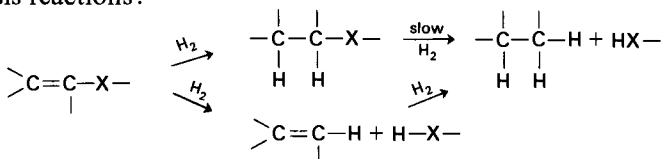
If carbon–carbon double bond saturation occurs first, the hydrogenolysis step will proceed relatively slowly or not at all. Conversely, if the carbon–carbon double bond is hindered, and consequently reduced slowly, hydrogenolysis might be expected to be extensive. Quantitative yields of cyclohexylacetic acid (XLIII) were obtained from hydrogenation of the vinyl lactone (XLII) over platinum oxide in ethanol (Newman and VanderWerf, 1945). Hydrogenolysis is characteristic of enolic lactones (Noland et al., 1959; Filler et al., 1961; Blomquist et al., 1961; Blomquist and Jaffe, 1958).

(XLII)   2H₂ →   (XLIII)
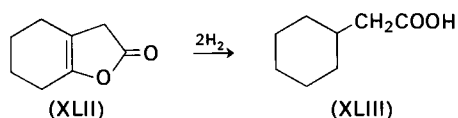
Prediction of the extent of hydrogenolysis is made particularly difficult, for minor structural changes in the substrate may drastically alter the relative rates of competing reactions. Hydrogenation of XLIV over platinum oxide gave the hydrogenolysis product (XLV) in 63 % yield, whereas hydrogenation of XLVI gave the saturated ether (XLVII) in 89 % yield. Probably the presence of the halogen so impeded saturation of the olefinic function that hydrogenolysis of the vinylic oxygen took precedence (Schweizer and Parham, 1960). Hydrogenolysis of XLIV may also have been facilitated by liberated hydrogen chloride.

(XLIV)   PtO₂ →   CH₃CH₂CH₂CH₂CH₂CH₂OH
                    (XLV)

(XLVI)   PtO₂ →   (XLVII)
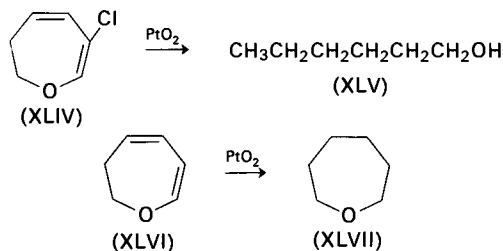
A. CATALYSTS

The generality governing the relationship between catalytic metal and the course of reduction of vinyl compounds seems clear and consistent: platinum always favors hydrogenolysis, palladium favors hydrogenation, and, judging by limited data, rhodium and ruthenium favor hydrogenation, perhaps even more than palladium.* These trends in catalyst performance are of course only relative; the substrate may be of such a structure that the reduction will follow only one course regardless of catalyst (Wenkert et al., 1961, Fajkos, 1958).

Reduction of cyclohexenyl acetate over palladium-on-calcium carbonate afforded cyclohexyl acetate and over platinum oxide cyclohexane (Fajkos,

* This generality is also applicable to phenols, if phenol is viewed as a vinyl alcohol.

1958). Platinum oxide also caused extensive hydrogenolysis of cholestenone enol acetate and enol benzoate, and of cyclohexenyl acetate and benzoate in ethanol and in acetic acid (Inhoffen *et al.*, 1950). Alkyl β-phenoxyvinyl ketones were reduced over palladium-on-barium sulfate in ethyl ether to the corresponding saturated ketone, whereas over platinum the phenol was formed through hydrogenolysis (Nesmeyanov *et al.*, 1955).
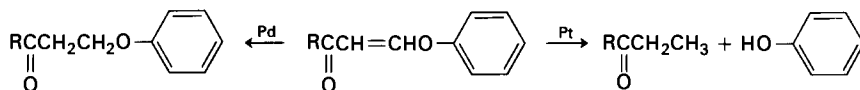
A similar difference between platinum and palladium was found in the reduction of an enol lactone (XLVIII). Reduction of this compound in ethanol over 10% palladium-on-carbon decreased in rate appreciably after absorption of one equivalent of hydrogen, and a dihydro compound (XLIX) was isolated. In contrast, reduction over platinum oxide in acetic acid led to the hexahydro hydrogenolysis compound (L) (Smyrniotis *et al.*, 1958). The solvent too may have influenced the course of this reduction.
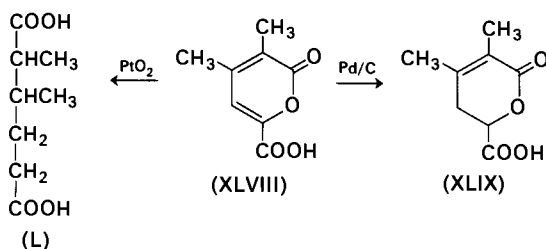
An unusually thorough study of the effects of catalysts and conditions on the products of hydrogenation has been made in an investigation of the properties of bifurandione. Bifurandione (LI) is structurally both an α,β-unsaturated ester and an enol ester and can exist in *cis* and *trans* forms. The products of reduction apparently depend on whether hydrogenation or hydrogenolysis is the primary reaction. Reduction of *trans*-bifurandione over platinum oxide in acetic acid containing a few drops of hydrochloric
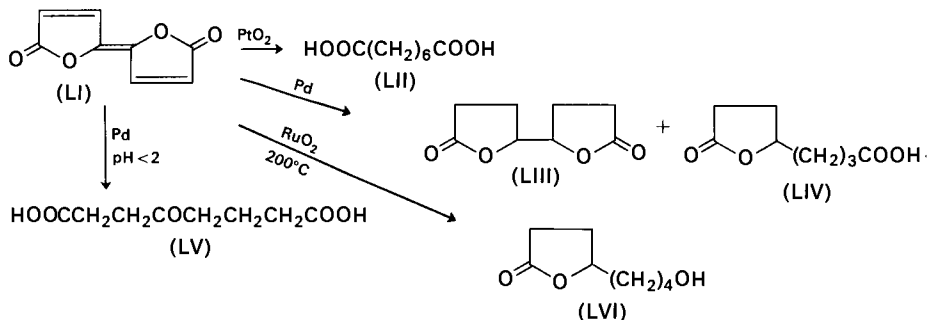
acid gave suberic acid (LII) in 87% yield (Sauer *et al.*, 1959). Reduction over palladium gave a mixture of bibutyrolactone (LIII) and γ-(γ-carboxypropyl)-butyrolactone (LIV) in ratios that depended on the carrier and conditions. Reduction over palladium-on-alumina gave LIII in 83% yield, over 10% palladium-on-carbon LIV in 69% yield. The reductions over 10% palladium-on-carbon to a mixture of LIII and LIV can be effected in neutral solvent as well as in acetic acid but, if the reaction medium were brought below pH 2 by addition of hydrochloric acid, 4-oxooctanedioic acid (LV) was obtained in 72% yield. At 200°C, reduction of bifurandione over ruthenium dioxide in dioxane afforded γ-(δ-hydroxybutyl)butyrolactone (LVI) (Holmquist *et al.*, 1959).

Rhodium and Ruthenium

There is very little in the literature on the use of rhodium and ruthenium for reduction of vinyl compounds, but several reports suggest that these catalysts may be worthy of consideration, especially when hydrogenolysis is to be avoided. In tests of several metals for hydrogenation of isopropenyl methyl ether, rhodium was found to be the most active; palladium was about half as active as rhodium. Platinum and ruthenium were almost inactive (Howard and Brown, 1961). Rhodium proved useful in the reduction of the enol acetate, 3-acetoxycholest-2-ene (LVII), to the saturated acetate (LVIII). Over platinum oxide the reduction had proved impossible, as only hydrogenolysis occurred, but over rhodium-on-alumina sufficient saturated ester could be obtained. Deuteration of LVII over rhodium led to about equal amounts of the 2- and 4-deuterated products; presumably the double bond had migrated on the catalyst (Cookson *et al.*, 1962).

(LVII)   (LVIII)
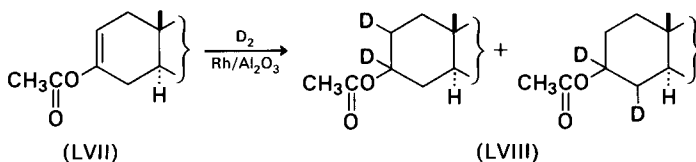
Amide vinylogs are cleaved by platinum oxide or Raney nickel to the amine. Vinylogs of *N*-acylamides are more resistant to cleavage and can be reduced at the olefinic linkage (Baker and Schlesinger, 1946; Kochetkov, 1954). Reduction of the amide vinylog (LIX) over palladium also led to cleavage products, but the amine alcohol could be obtained in 71% yield by reduction over rhodium and in 72% yield by reduction over ruthenium. A

(LIX)   (LX)
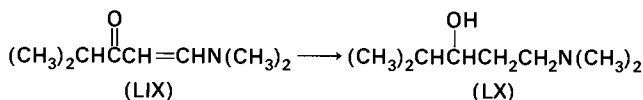
solution of 50 gm LIX in 200 ml water was reduced over 2 gm 5% ruthenium-on-carbon at 70°C and 1500 psig for 2 hours. Distillation of the product afforded LX in 72% yield (Martin *et al.*, 1966).

B. Enol Phosphate Esters

On hydrogenation, enol phosphate esters show the same discrimination between palladium and platinum catalysts as enol esters of carboxylic acids; palladium favors hydrogenation, platinum hydrogenolysis. Reduction of diethyl isopropenyl phosphate over 10% palladium-on-carbon in ethyl acetate afforded, after absorption spontaneously stopped, diethyl isopropyl phosphate in 70% yield. On the other hand, two moles of hydrogen were absorbed in hydrogenation over platinum oxide, and diethyl hydrogen phosphate was isolated in 60% yield (Jacobson *et al.*, 1957).

$$\text{HOOP(OEt)}_2 \xleftarrow[\text{2H}_2]{\text{Pt}} \underset{\text{CH}_2=\text{CCH}_3}{\overset{\text{OPO(OEt)}_2}{|}} \xrightarrow[\text{H}_2]{\text{Pd}} \underset{\text{CH}_3\text{CHCH}_3}{\overset{\text{OPO(OEt)}_2}{/}}$$
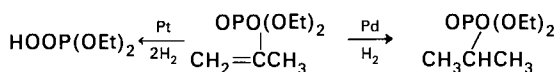
C. Hydroxymethylene Compounds

Hydrogenolysis of hydroxymethylene derivatives affords a method of introducing a methyl group into carbonyl systems. Reduction of LXI to LXII illustrates the procedure for both a ketone and lactone (Knox *et al.*, 1961).
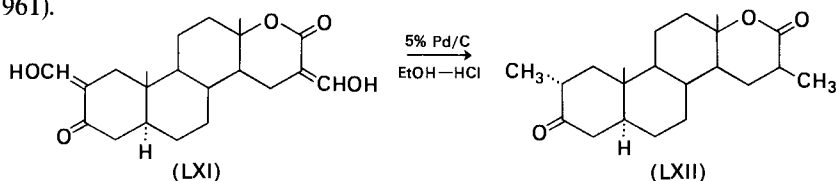
Hydroxymethylene compounds need not necessarily undergo hydrogenolysis. Reduction of a ketonic hydroxymethylene compound (LXIII) over either platinum oxide or Raney nickel in ethanol led to the dihydro derivative (LXIV) in which both oxygen atoms were retained. Hydrogenolysis to LXVI

| (LXIII) | R = H | (LXIV) | R = OH |
| (LXV) | R = —OCC₆H₅ | (LXVI) | R = H |
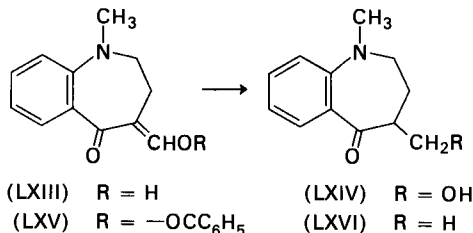
was effected by converting the hydroxymethylene compound to the corresponding benzoate (LXV), and carrying out the reduction over platinum oxide in ethanol (Astill and Boekelheide, 1955). The technique of achieving hydrogenolysis through esterification of the enol has been employed successfully also in the steroid field with enols that without esterification were converted to the alcohol (Harnik, 1963).

IV. DEBENZYLATION

Benzyl-type compounds usually undergo hydrogenolysis readily,

$$\langle\!\bigcirc\!\rangle\!-\!CH_2\!-\!X \;+\; H_2 \;\longrightarrow\; \langle\!\bigcirc\!\rangle\!-\!CH_3 \;+\; HX$$
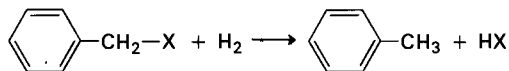
where X = halogen, NH_2, NHR, NR_2, OH, OR, OCOR, etc. Hydrogenolysis occurs easily because of the activating influence of the aromatic ring, and it is important to choose catalysts and conditions such that ring saturation does not precede hydrogenolysis. If the aromatic ring is reduced first, hydrogenolysis will occur with great difficulty if at all. (Conditions for ring saturation without hydrogenolysis are described in the chapter on hydrogenation of carbocyclic aromatics.) Hydrogenolysis of benzyl groups attached to oxygen, nitrogen, or sulfur has been reviewed admirably by Hartung and Simonoff (1953). The review encompasses a discussion of the scope and limitations of the reduction, experimental conditions and catalysts, and an extensive tabular survey of benzyl compounds that have been subjected to hydrogenolysis.

A. Benzyl Groups Attached to Oxygen

Hydrogenolysis of benzyl alcohols, ethers, esters, acetals, and phosphates can all be achieved readily over platinum metal catalysts.

1. Catalysts

Palladium, platinum, rhodium, nickel, and copper-chromium oxide catalysts have all been used successfully in debenzylations, but palladium is by far the most favored catalyst. Palladium combines a high activity for debenzylation with a low tendency to saturate the aromatic ring. Tables III and IV give a comparison of the rates of hydrogenation of benzyl alcohol and benzyl acetate over 5% palladium-, platinum-, rhodium-, and ruthenium-on-carbon in various solvents (Rylander and Steele, 1965). Many of the

reductions proceeded at a constantly declining rate, which may be due in part to inhibition by products of the reduction. It was shown earlier that the declining rate in hydrogenolysis of benzyl acetate over palladium was caused by inhibition by the toluene formed during the reduction (Meschke and Hartung, 1960).

TABLE III

HYDROGENATION OF BENZYL ALCOHOL[a]

Solvent	Time (in minutes) for 50% completion[b]			
	5% Pd/C	5% Pt/C	5% Rh/C	5% Ru/C
Water	120	>240(25%)	>240(42%)	>240(25%)
Acetic acid	15	>240(15%)	70	>240(4%)
Methanol	160	>240(0%)	40	>240(0%)
Ethyl acetate	>240(6%)	>240(20%)	>240(22%)	>240(0%)
Hexane	>240(0%)	>240(0%)	180	>240(0%)
Water + $HClO_4$	28	>240(30%)	130	>240(0%)

[a] 500 mg 5% metal-on-carbon, 34 mmoles benzyl alcohol, and 100 ml solvent at atmospheric pressure, room temperature; percentages indicate the percent of one equivalent of hydrogen absorbed in 240 minutes.
[b] Absorption of one half an equivalent of hydrogen.

TABLE IV

HYDROGENATION OF BENZYL ACETATE[a]

Solvent	Time (in minutes) for 50% completion[b]		
	5% Pd/C	5% Pt/C	5% Rh/C
Water	35	150	60
Acetic acid	10	165	5
Methanol	13	>240(2%)	11
Ethyl acetate	6	>240(16%)	65
Hexane	>240(3%)	>240(45%)	>240(2%)

[a] 500 mg 5% metal-on-carbon, 28 mmoles of benzyl acetate and 100 ml solvent at atmospheric pressure, room temperature; percentages indicate the percent of one equivalent of hydrogen absorbed in 240 minutes.
[b] Absorption of one half an equivalent of hydrogen.

The rates of reduction of benzyl alcohol and benzyl acetate vary drastically with the catalyst and solvent. Palladium is in general by far the most active catalyst, although satisfactory rates may be obtained over rhodium and platinum in appropriate solvent. The latter catalysts may cause some ring reduction, which was not measured in the experiments of Tables III and IV.

The extent of hydrogenolysis of benzyl alcohol and benzyl acetate varies greatly with the catalyst (Table V). Ruthenium under vigorous conditions gave mostly cyclohexylcarbinol and cyclohexyl acetate, whereas reduction over rhodium-, palladium-, or platinum-on-carbon afforded primarily the hydrogenolysis products, toluene and methylcyclohexane.

TABLE V

HYDROGENATION OF BENZYL ALCOHOL AND
BENZYL ACETATE IN WATER[a]

Catalyst	Percent hydrogenolysis[b]	
	Benzyl alcohol	Benzyl acetate
5% Pd/C	100	100
5% Pt/C	100[c]	73
5% Rh/C	80–90	82
5% Ru/C	25	24

[a] Pressure = 750 psig, temperature = 100°C; 15 ml substrate, 15 ml water.
[b] Percent hydrogenolysis =

$$\frac{\text{moles[toluene + methylcyclohexane]} \times 100}{\text{moles[toluene + methylcyclohexane + cyclohexylcarbinol (or acetate)]}}.$$

[c] Poisoned before completion.

The work of Sowden and Kuenne (1952) provides an interesting example of how the course of reduction of a benzyl acetal may be changed by the catalyst and solvent. Hydrogenation of 1,2-benzylidene-D-glucofuranose (LXVII) over platinum oxide in acetic acid afforded the hexahydrobenzylidene (LXVIII) in 88% yield, but reduction of LXVII over "S-palladium-black" (Kindler *et al.*, 1949) in ethanol resulted in the hydrogenolysis product, glucose. It may have been expected, from the earlier work of Richtmyer (1934) on hydrogenation of glycosides, that platinum would favor ring saturation and palladium hydrogenolysis, but the high selectivity observed in hydrogenation of LXVII is surprising. Richtmyer found varying degrees
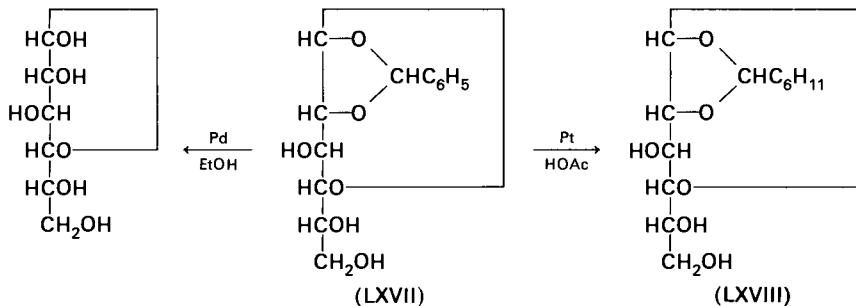
of hydrogenolysis of phenyl and benzyl glycosides over platinum catalysts with extensive hydrogenolysis in the presence of a trace of hydrochloric acid. Ring saturation of benzyl ethers over platinum oxide without hydrogenolysis has been reported by Hurd and Jenkins (1966).

2. Benzyl Alcohols

Benzyl alcohols are reduced easily to the hydrocarbon. The reduction is usually carried out over palladium catalysts in alcohol or in alcohol or acetic acid containing small amounts of strong mineral acids (Hartung and Simonoff, 1953). Strong acids are promoters in the reduction and could in some cases possibly catalyze dehydration to the olefin, which would then be rapidly reduced. However, hydrogenolysis of LXIX was shown not to occur by this pathway. Reduction of LXIX over 10% palladium-on-carbon in ethyl acetate containing perchloric acid gave LXX with the trans configuration preserved. Hydrogenolysis must have proceeded directly without dehydration to the corresponding olefin, inasmuch as the olefin on reduction gave the cis isomer (Gutsche et al., 1961).

(LXIX)   (LXX)
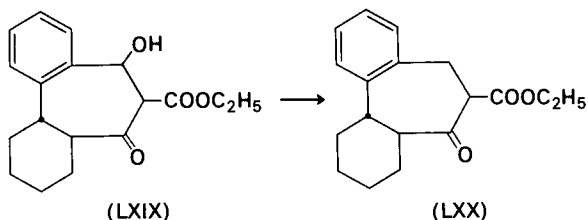
On the other hand, catalytic reduction of the benzyl alcohol function in tetracycline over palladium-on-carbon evidently removed the C-6 hydroxyl by dehydration rather than by hydrogenolysis. This dehydration reaction is normally acid-catalyzed, but in the absence of palladium and hydrogen did not proceed at a measurable rate under the mildly acid conditions of the hydrogenolysis.* Hydrogenations in this series, which were discussed in some detail, were carried out under unusual conditions. The reaction medium consisted of one mole of boric acid per mole of tetracycline, enough hydrochloric acid to give a pH of 1.8, and 1:1 dimethylformamide–water solvent. The boric acid served to modify the nature of the reaction by-products (McCormick et al., 1960).
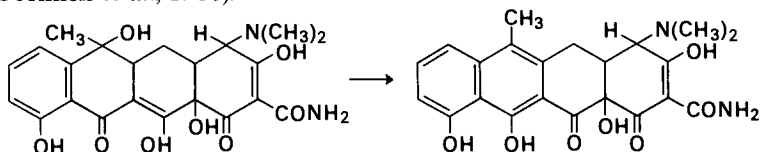
* Other workers also have noted the promotion of normally acid-catalyzed reactions over hydrogenation catalysts in the presence of hydrogen (Caldwell and Jones, 1946).

Rhodium proved to be a useful catalyst for hydrogenolysis of the benzyl alcohol function in the tetracycline series. A slurry of 10 gm 6-demethyl-chlorotetracycline (LXXI) in 240 ml dimethylformamide and 3.5 ml hydrochloric acid, reduced over 10 gm 30% rhodium-on-carbon, afforded 6-deoxy-6-demethylchlorotetracycline (LXXII) (Fields *et al.*, 1961). The reduction is noteworthy in that the chlorine atom survived. Other reductions in this series over rhodium catalysts have been described by McCormick and Jensen (1962).

(LXXI) → (LXXII)
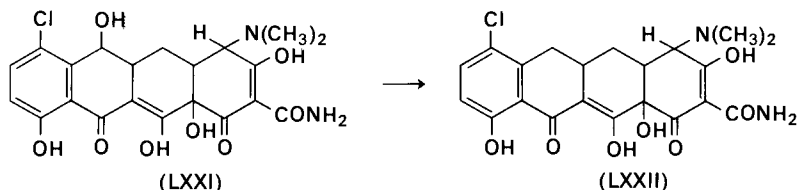
Hydrogenolyses of benzyl alcohols carried out at elevated temperatures may be accompanied by various side-reactions. Catalytic hydrogenation of phenylcarbinols at 250°C over palladium- or platinum-on-carbon gave the hydrocarbon plus small amounts of ketone. Hydrogenolysis of benzyl alcohol gave 35–65% toluene plus benzene through decarbonylation of benzaldehyde. Aliphatic alcohols are not reduced under these conditions but give instead aldehydes and ketones (Shuikin and Bel'skii, 1959).

3. Benzyl Ethers and Esters

In general, benzyl esters are cleaved somewhat more easily than the corresponding benzyl ethers, and the difference in reactivity has been used as a method of removing two benzyl-type protecting groups one at a time (Conrad and Dec, 1958). Hydrogenolyses are most often carried out over palladium catalyst in alcohol or acetic acid frequently containing small amounts of mineral acid (Hartung and Simonoff, 1953). Acid may change the course of reduction; hydrogenation of esters of mandelonitrile over palladium-on-carbon in the presence of strong mineral acids gave high yields of phenylethylamine; when the acid was omitted the principal product was benzyl cyanide (Kindler and Schrader, 1949). Benzyl cyanides were formed also in hydrogenolysis of O-carbethoxymandelonitriles in neutral media (Kindler and Schrader, 1950).
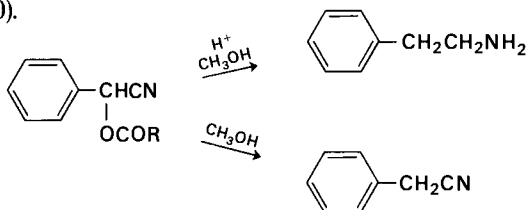
Most hydrogenolyses of benzyl ethers or esters are carried out to remove the benzyl function that has served as a protecting group during a synthesis, but these hydrogenolyses may also have synthetic value in their own right. 5-Phenylpentanol was isolated in 72% yield after hydrogenolysis of 9 gm 2-phenyltetrahydropyran in 40 ml acetic acid containing 2.5% of 60% perchloric acid. The reduction, carried out at 3 atm over 1 gm 5% palladium-on-carbon, was complete in 35 minutes. Hydrogenolysis of phenyldioxane (LXXIII) over palladium-on-carbon in acetic acid containing 2% sulfuric acid afforded LXXIV in 75% yield (Baker *et al.*, 1948). Similar reductions of diphenyldioxanes were conveniently carried out over palladium-on-barium sulfate at 90°C (Stumpf, 1953).

(LXXIII)   (LXXIV)
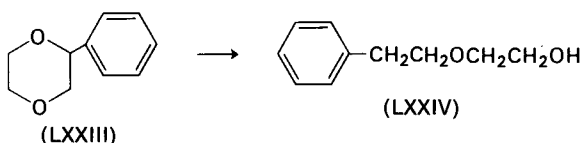
4. Selectivity

It is difficult to generalize as to what functions will survive unchanged the hydrogenolysis of benzyl-type groups attached to oxygen. Benzyl groups have undergone hydrogenolysis, leaving unchanged aromatic ketones (Bonner *et al.*, 1964; Moffett *et al.*, 1964), aromatic halogen (Lawson *et al.*, 1960; Newman and Wiseman, 1961; Dürckheimer and Cohen, 1964), amine oxides (Lott and Shaw, 1949), nitriles (Kindler and Schrader, 1949, 1950), and olefins (McQuillin and Simpson, 1963). Selectivity is undoubtedly related to the relative accessibility of the catalyst to each function, but that is not always easily determined.

5. Carbobenzyloxy Compounds

The carbobenzyloxy radical is widely used as a protecting group in organic synthesis. An advantage is that it can be removed easily by hydrogenolysis under the mildest conditions, often without disruption of other portions of the molecule. It should be noted that the course of this hydrogenation cannot be followed by pressure decrease, unless the reduction is carried out in the presence of alkali, inasmuch as a mole of carbon dioxide is liberated for each mole of hydrogen consumed. The extent of hydrogenolysis is followed at times by measuring the carbon dioxide liberated. Palladium, supported or unsupported, is the best catalyst for this hydrogenolysis and is used by most investigators.

Hydrogenolysis of carbobenzyloxy compounds has been widely employed in the synthesis of peptide linkages (Bergmann and Zervas, 1932). The amino group of an amino acid is protected by interaction with carbobenzyloxy

chloride, forming a benzyl carbamate that remains unchanged while the free carboxyl group is converted to an acid chloride. Reaction of the acid chloride and another amino acid establishes the peptide linkage. Hydrogenolysis, which affects only the protecting group, yields toluene and a carbamic acid that spontaneously loses carbon dioxide.

$$C_6H_5CH_2OCONHCHRCONHCHR'COOH \longrightarrow$$

$$NH_2CHRCONHCHR'COOH + C_6H_5CH_3 + CO_2$$
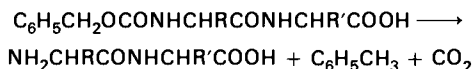
Palladium, as palladium black or palladium-on-carbon, is usually used in these hydrogenolyses, in an alcohol solvent frequently acidified by acetic acid or hydrogen chloride (Hartung and Simonoff, 1953). Derivatives of carbobenzyloxy chloride have been used to advantage in peptide synthesis. p-Bromobenzyl carbamates often have higher melting points and crystallize better than the corresponding benzyl carbamates (Channing et al., 1951). The p-nitrocarbobenzyloxy radical has been used in the preparation of peptides containing cystine or cysteine; this radical is more labile* and undergoes hydrogenolysis over palladium in the presence of toxic sulfur atoms (Berse et al., 1957), whereas the unsubstituted carbobenzyloxy group does not (White, 1934). Hydrogenation of di-p-nitrocarbobenzyloxy-L-cystine (0·599 gm) was carried out over 250 mg 10% palladium-on-carbon in 40 ml 0·05 N NaOH. Six moles of hydrogen were absorbed in 6 hours and, after removal of the catalyst and p-tolylhydroxylamine by filtration, the solution was acidified to pH 5 with hydrochloric acid. After concentration, L-cystine crystallized in practically quantitative yield. When the reduction was allowed to continue another 10 hours, the hydrochloride of L-cysteine could be obtained in 90% yield. It is of incidental interest that the reduction of the nitro group was arrested at the hydroxylamine stage in this system. Hydrogenolysis of the carbobenzyloxy group in N-carbobenzyloxyamino acids and N-carbobenzyloxy dipeptides has been achieved by refluxing the substrate with triethylsilane in the presence of palladium chloride and triethylamine (Birkofer et al., 1961).

Carbobenzyloxy radicals have been used as protective groups in the synthesis of peptide-like condensates (LXXV) of amino acids and amino oxyacids.

$$C_6H_5CH_2OCONHCHRCOOH + NH_2OCH_2CO_2C_2H_5 \longrightarrow$$

$$C_6H_5CH_2OCONHCHRCONHOCH_2CO_2C_2H_5$$

(LXXV)
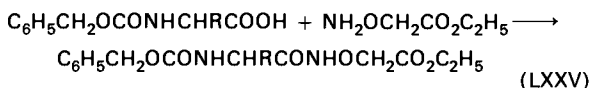
Coupling was achieved best by the dicyclohexylcarbodiimide procedure (Sheehan and Hess, 1955). Hydrogenolysis over 10% palladium-on-carbon resulted first in cleavage of the benzyl–oxygen bond and, if the reduction were

---

* The labilizing effect of the p-nitro group also extends to S-benzyl derivatives; S-p-nitrobenzylcysteine was reduced to cysteine over 10% palladium-on-carbon, whereas S-benzylcysteine could not be (Berse et al., 1957).

continued, in cleavage of the amido-oxy peptide linkage to an amino acid and glycolic acid ester:

$$LXXV \longrightarrow NH_2CHRCONHOCH_2COOC_2H_5 \longrightarrow$$
$$(LXXVI)$$
$$NH_2CHRCONH_2 + HOCH_2COOC_2H_5$$
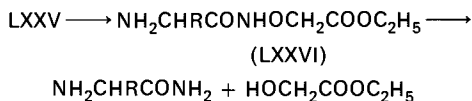
Hydrogenolysis of the ester proceeded 5–6 times more rapidly than hydrogenolysis of the free acid. On the basis of this and other findings, the authors offered the generalization that the ease of hydrogenolysis of the amido-oxy linkage depends on the amount of enol ion present:

$$\overset{\overset{O}{\|}}{-C}-NH-O- \rightleftharpoons \overset{\overset{O^-}{|}}{-C}=N-O- \longleftrightarrow \overset{\overset{O^+}{\|}}{-C}-\overset{}{N}-O-$$
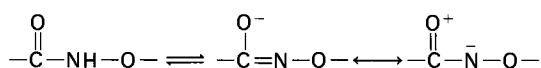
The amido-oxy group of the ester (LXXVI) is charged, forms an internal salt with the adjacent α-amino group, and is thus easily reduced. In the free acid both the carboxylic and amino groups participate in internal salt formation, the amido-oxy group consequently remains uncharged, and hydrogenolysis is accordingly more difficult. The same effect may be achieved by elimination of the enolic charge in the amido-oxy group of the ester (LXXVI) by addition of hydrochloric acid; the hydrochloride salt is much more difficult to reduce (Frankel *et al.*, 1964).

A novel procedure for synthesis of acylated α-amino acid and polypeptide hydrazides has been developed by Hofmann *et al.* (1952). The method involves synthesis of α-amino acid carbobenzyloxyhydrazides and their incorporation into polypeptide derivatives, followed by liberation of the hydrazide group through hydrogenolysis of the protecting carbobenzyloxy function. Hydrogenolyses were carried out over palladium sponge in alcoholic hydrochloric acid. This method of synthesis allows introduction of a potential hydrazide group into a peptide moiety at the monoamino acid stage, and avoids exposure of complex sensitive peptides to hydrazine.

Carbobenzyloxy protecting groups have proved of use also in the synthesis of amino sugar. The following example is of particular interest because of the experimental technique. Methyl 3,4,6-tri-*O*-acetyl-2-amino-*N*-(benzyloxy-carbonyl)-2-deoxy-α-D-glucoside (LXXVII), 5 gm, was dissolved at 0°C in 75 ml dry methanol containing exactly 0.01104 mole of hydrogen chloride; 1 gm 10% palladium-on-carbon was added. (The authors at this point in the experimental section urge *caution*. Indeed, a fire is quite likely with this concentration and amount of metal. It would have been better to quickly add the solution to the catalyst or to pre-wet the catalyst with methanol before adding it to the reaction mixture.) A rapid stream of hydrogen was then passed into the solution through a sintered glass diffuser. The emergent gases were passed through limewater from time to time; the reduction was

completed in 165 minutes when carbon dioxide was no longer detectable. The authors comment that the use of a small vessel (100 ml) and a large (1 × 2 cm) gas diffuser appears to be essential if the reaction is to be completed in a reasonable time and without loss of acetyl groups (Wolfrom *et al.*, 1957).
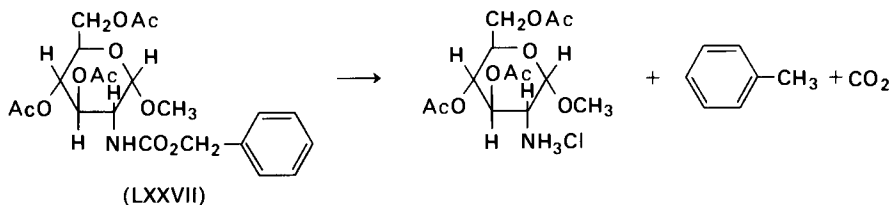
Hydrogenolysis of a series of diethyl carbobenzyloxyglycylaminomalonates (LXXVIII) provided a satisfactory method for preparing the corresponding 3-carbethoxy-2,5-piperazinediones (LXXIX).
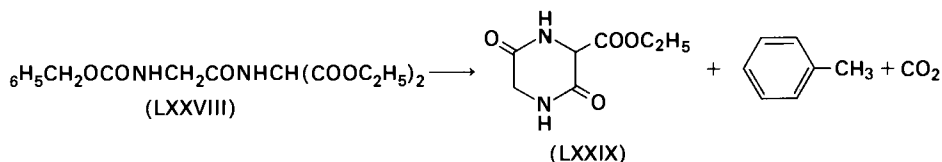
A typical hydrogenolysis was carried out with 0.05 mole of LXXVIII in 200 ml anhydrous ethanol at 30 psig and 70°C over 3 gm 5% palladium-on-carbon. The 3-carbethoxy-2,5-piperazinediones were obtained in 90–97% yield. In some instances, pretreatment of the alcoholic solution of LXXVIII with Raney nickel led to a smoother hydrogenolysis over palladium. The substrates were prepared by treatment of *N*-carbobenzyloxyglycyl chloride with two equivalents of diethyl aminomalonate; the latter compound was obtained by hydrogenation of the isonitrosomalonate in alcohol at 1800 psig over 20% palladium-on-carbon (Zaugg *et al.*, 1956).

The carboxybenzyloxy structure is present in the oxazolidinedione (LXXX), and hydrogenolysis of LXXX proceeded as expected with cleavage of the benzyl oxygen and liberation of carbon dioxide. A solution of 0.31 gm LXXX in 10 ml dioxane containing 0.60 gm 10% palladium-on-carbon was reduced in a microhydrogenator equipped with a potassium hydroxide tube to absorb liberated carbon dioxide. After 9 hours at atmospheric pressure the theoretical amount of hydrogen was absorbed, and phenaceturic acid anilide (LXXXI) was obtained in 92% yield. The oxazolidinedione ring system itself
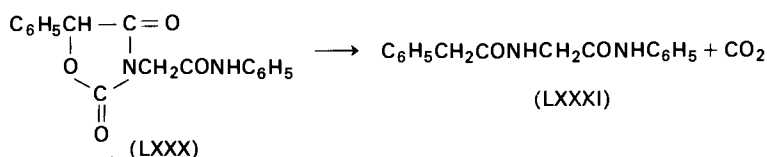
may function as a protecting group, and hydrogenolysis of suitable derivatives has been used to prepare β-lactam thiazolidines with the 6-phenylacetylamino group characteristic of benzylpenicillin (Sheehan and Laubach, 1951).

Hydrogenolysis of the carbobenzyloxy function of LXXXII provided a convenient synthesis of primocarcin (LXXXIII). Debenzylation of 3.0 gm LXXXII in 150 ml ethanol was carried out over 1 gm 10% palladium-on-strontium carbonate. When 1.1 moles of hydrogen had been absorbed, the rate fell from 135 to 5 ml/minute and hydrogenation was discontinued. The intermediate β-keto acid appeared to be relatively stable, and decarboxylation followed by dehydration occurred only on evaporation of the reaction solution (Bowman et al., 1965).

$$\underset{\text{(LXXXII)}}{C_6H_5CH_2OCO\underset{\underset{CH_2OH}{|}}{\overset{\overset{NHAc}{|}}{C}}CO(CH_2)_2CONH_2} \longrightarrow \underset{\text{(LXXXIII)}}{CH_2{=}\overset{\overset{NHAc}{|}}{C}CO(CH_2)_2CONH_2} + CO_2 + H_2O$$
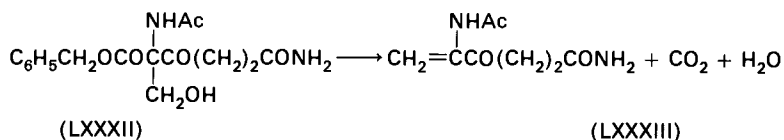
6. Hydrogenolysis of Phosphate Esters

Benzyl and phenyl esters of phosphoric acid are employed with much success in the synthesis of phosphorylated amines and alcohols (Atherton, et al., 1945a,b, 1948; Zervas, 1939; Wagner et al., 1963). The synthesis of phosphate esters of sugars nowadays generally employs dibenzyl- or diphenyl-phosphorochloridates, replacing the use of phosphorus oxychloride (Pigman, 1957). After suitable transformations, the protecting benzyl or phenyl radical is removed by hydrogenolysis. Palladium is employed invariably for hydrogenolysis of the benzyl group and platinum for hydrogenolysis of the phenyl group, a preference that finds direct parallel in hydrogenolysis of benzyl and phenyl esters of carboxylic acids.

a. Benzyl Esters. Palladium is the preferred catalyst for hydrogenolysis of benzyl phosphate esters, and selective cleavage of a benzyl radical in the presence of a phenyl phosphate is readily achieved (Tener and Khorana, 1958). Friedman and Seligman (1954) removed selectively the benzyl group of LXXXIV over palladium-on-carbon. A mixture of 4.3 gm crude LXXXIV was reduced over 0.5 gm palladium-on-carbon in 40 ml ethanol for 2.5 hours. The product (LXXXV) was isolated as a cyclohexylamine salt. Attempts to prepare di(2-chloroethyl)phosphoramidic acid (LXXXVI) by hydrogenolysis

(LXXXIV)   (LXXXV)   (LXXXVI)
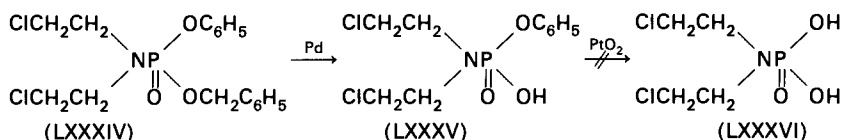
of LXXXV failed, as did other attempts (Friedman *et al.*, 1954) by hydro-
genolysis of the dibenzyl derivative. Apparently the product is too unstable
to isolate readily. Phenyldiamidophosphonate (LXXXVII), however, under-
went hydrogenolysis readily over platinum oxide, and afforded LXXXVIII
in 80% yield isolated as a cyclohexylamine salt.

$$\begin{array}{ccc}
\text{ClCH}_2\text{CH}_2 & \text{OC}_6\text{H}_5 \\
\diagdown\!\!\!\diagup \text{N} \text{P} \diagdown \\
\text{ClCH}_2\text{CH}_2 \quad \text{O} \quad \text{NH}_2
\end{array}
\longrightarrow
\begin{array}{ccc}
\text{ClCH}_2\text{CH}_2 & \text{OH} \\
\diagdown\!\!\!\diagup \text{N} \text{P} \diagdown \\
\text{ClCH}_2\text{CH}_2 \quad \text{O} \quad \text{NH}_2
\end{array}$$

(LXXXVII)   (LXXXVIII)
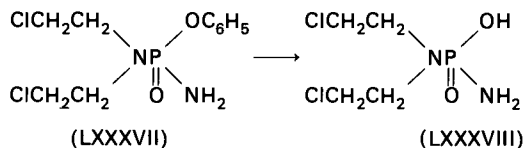
Both benzyl groups of dibenzyl 3,5-dibromo-4-hydroxyphenyl phosphate
(LXXXIX) could be removed by hydrogenolysis over 10% palladium-on-
carbon in methanol without appreciable debromination. A solution of
15.2 gm LXXXIX in 250 ml absolute methanol containing 1.5 gm 10%
palladium-on-carbon absorbed two equivalents of hydrogen in 14 minutes.
It was essential to interrupt the reduction at this point to prevent debromina-
tion. The phosphate (XC) was isolated in 67% yield (Dürckheimer and
Cohen, 1964).

$$O \leftarrow P(OBz)_2 \qquad\qquad O \leftarrow P(OH)_2$$

(LXXXIX)   (XC) $+ \; 2C_6H_5CH_3$
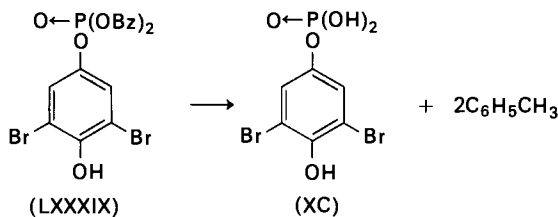
Hydrobenzoin cyclic phosphate (XCI) has been recommended as a
phosphorylation reagent (Ukita *et al.*, 1958) inasmuch as it, in common with
other cyclic phosphates of diols, undergoes a facile alcoholysis in the presence
of trifluoroacetic acid or hydrogen chloride as catalyst. The intermediate
(XCII) is relatively stable toward further alcoholysis when trifluoroacetic
acid is used. Hydrogenolyses of XCII were carried out as the ammonium
salt over 10% palladium-on-carbon.

$$\begin{array}{c}
\text{C}_6\text{H}_5\text{CH}-\text{O} \\
\qquad\quad | \qquad\;\; \text{P} \\
\text{C}_6\text{H}_5\text{CH}-\text{O} \quad \text{OH}
\end{array}
+ \text{ROH} \longrightarrow
\begin{array}{c}
\text{C}_6\text{H}_5\text{CHOH} \\
\qquad\qquad | \quad \text{O} \\
\text{C}_6\text{H}_5\text{CHOPOR} \\
\qquad\qquad\quad | \\
\qquad\qquad\quad \text{OH}
\end{array}
\xrightarrow{\text{H}_2}
\begin{array}{c}
\text{O} \\
\| \\
\text{HOP}-\text{OR} \\
| \\
\text{OH}
\end{array}$$

(XCI)   (XCII)
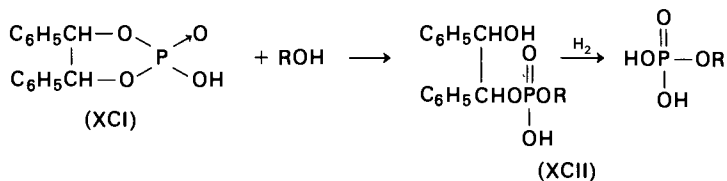
Di-*p*-nitrobenzyl- and di-*p*-iodobenzylphosphoryl chlorides have been
recommended as phosphorylation reagents. They are more stable than di-
benzylphosphoryl chloride, and give derivatives of lower solubility and

higher stability. Hydrogenolysis of the nitrobenzyl derivatives is accompanied by reduction of the nitro group to an amine (Zervas and Dilaris, 1955).

As might be expected, palladium is an excellent catalyst also for hydrogenolysis of phosphorus-containing benzyl esters, when the ester is remote from the phosphorus atom (Lies et al., 1953). The benzyl ester function of XCIII underwent a very rapid hydrogenolysis over 10% palladium-on-carbon in ethanol (Magerlein and Kagan, 1960).

$$
\begin{array}{ccc}
COOCH_2C_6H_5 & & COOH \\
| & & | \\
CH_2 & \longrightarrow & CH_2 \\
| & & | \\
O{=}P{-}(OC_3H_7)_2 & & O{=}P{-}(OC_3H_7)_2 \\
(XCIII) & &
\end{array}
$$
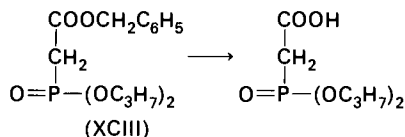
b. Phenyl Esters. Hydrogenolysis of phenylphosphates is carried out usually over platinum oxide (Reithel and Claycomb, 1949; Baer and Kates, 1950; Maley et al., 1956; Kilgour and Ballou, 1958; Ballou and Fischer, 1955, 1956; Baer and Maurukas, 1952; Griffin and Burger, 1956; Ukita and Hayatsu, 1962). The phosphorus moiety seems to activate the carbon–oxygen bond toward hydrogenolysis, for apparently cleavage is usually complete and must have preceded saturation of the phenyl ring, inasmuch as alkyl phosphates are stable toward hydrogenolysis. Iridium seems never to have been used in this type of reduction but might prove useful, as the tendency of iridium to promote hydrogenolysis of a phenyl–oxygen bond is at times as great or greater than that of platinum (Rylander and Steele, 1965).

2-Phosphoryl-D-glyceric acid (XCV) was prepared by stepwise hydrogenolysis of methyl 3-O-benzyl-2-diphenylphosphoryl-D-glycerate (XCIV). The success of this reduction depended on the use of an active platinum catalyst active enough to remove the phenyl groups in 1.5 hours or less; a slower reduction resulted in considerable phosphate migration. The benzyl group was first removed by reducing 5.0 gm XCIV over 5 gm 5% palladium-on-carbon (freed of acid by washing) in 100 ml absolute ethanol. Hydrogenolysis was complete in 10–15 minutes. The palladium catalyst was removed by centrifugation, and 1.0 gm freshly prepared platinum oxide was added to the reaction along with 1.0 gm acid-washed charcoal to prevent clumping, which otherwise occurred. Eight moles of hydrogen were absorbed within an hour and the reduction was discontinued (Ballou and Fischer, 1954). The hydrogenolysis reaction itself may have been completed sooner.

$$
\begin{array}{ccccc}
OCH_3 & & OCH_3 & & ONa \\
| & & | & & | \\
C{=}O & \xrightarrow{Pd} & C{=}O & \xrightarrow[\text{(2) NaOH}]{\text{(1) PtO}_2,\text{H}_2} & C{=}O \\
| & & | & & | \\
HC{-}OPO_3(C_6H_5)_2 & & HC{-}OPO_3(C_6H_5)_2 & & HCOPO_3Na_2 \\
| & & | & & | \\
H_2C{-}OCH_2C_6H_5 & & H_2COH & & H_2COH \\
(XCIV) & & H_2COH & & (XCV)
\end{array}
$$
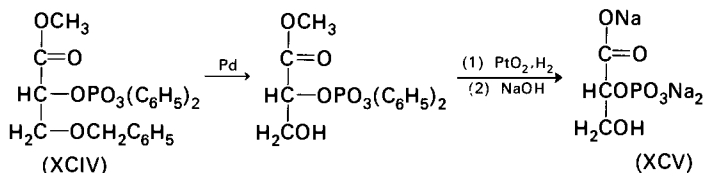
In other reactions better results have been obtained by the concurrent removal of protective groups. The consecutive removal of the carbobenzyloxy and phenyl groups of XCVI did not give as good results as removal of both together over a mixture of platinum and palladium catalysts (Baer *et al.*, 1952).

$$
\begin{array}{cc}
& OC_6H_5 \qquad\quad O \\
& \quad | \qquad\qquad\; \| \\
H_2C-O-P-OCH_2CH_2NHC-OCH_2C_6H_5 \\
\quad | \qquad \| \\
\quad | \qquad O \\
HCOOCR \\
\quad | \\
H_2COOCR
\end{array}
$$

$$
\begin{array}{c}
\qquad\qquad O \\
\qquad\qquad \| \\
H_2C-OP-OCH_2CH_2NH_2 \\
\quad | \;\; \| \\
\quad | \;\; O \\
HCOOCR \\
\quad | \\
H_2COOCR
\end{array}
$$
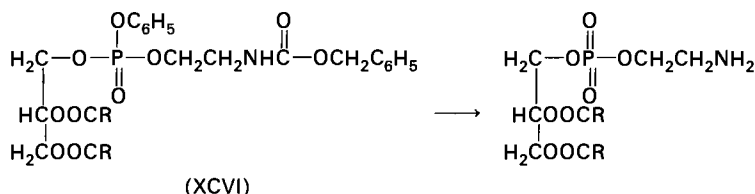
(XCVI)

The synthesis of glucosamine 3-phosphate (XCVIII) by hydrogenolysis of XCVII is particularly interesting, in that it involves cleavage of four different types of protective group. The use of strong acids that displace the phosphoric ester group from C-3 to C-6 was avoided throughout the sequence. The protective benzyl ether, benzyl acetal, and carbobenzyloxy functions were removed by hydrogenolysis of XCVII over palladium black in water at 50°C and, finally, after addition of acetic acid, at 60°C. Hydrogenolysis of the phenyl groups in the resulting crude glucosamine 3-diphenylphosphate was accomplished over platinum black at room temperature in absolute alcohol. The yield of XCVIII from XCVII was 25–30% (Westphal and Stadtler, 1963).

(XCVII)   (XCVIII)
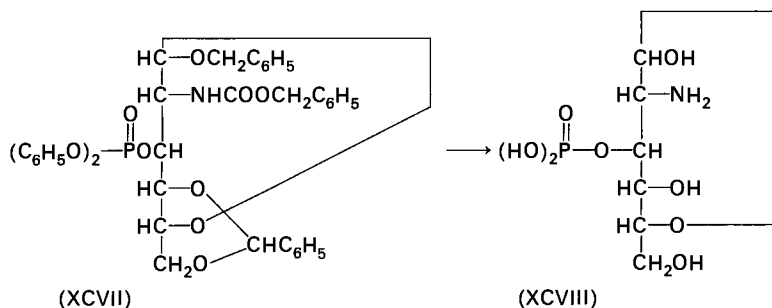
7. Stereochemistry of Hydrogenolysis

Hydrogenolysis of benzyl alcohols and benzyl ethers occurs largely with retention of configuration over nickel (Bonner *et al.*, 1952; Bonner and Zderic, 1956; Zderic *et al.*, 1960; Garbisch, 1962; Mitsui, *et al.*, 1964) and with inversion over palladium-on-carbon. Optically active methyl β-hydroxy-β-phenyl-butyrate, 3-phenylbutane-1,3-diol, methyl γ-hydroxy-γ-phenylvalerate, 4-phenylpentane-1,4-diol, and 2-methyl-2-phenyltetrahydrofuran were each reduced over Raney nickel and over 5% palladium-on-carbon in ethanol. Optical purity was maintained in 82–96% over nickel and in 70–100% over palladium, nickel affording the product with retained configuration, palladium the product with inverted configuration. These differences were

accounted for by assuming that the reacting molecules were adsorbed on the two catalysts in different configurations. Over nickel, which has a greater affinity for oxygen than palladium, the benzyl oxygen atom is adsorbed on the nickel surface and hydrogenolysis proceeds stereospecifically by an S_N1 type of mechanism. Over palladium, the benzyl oxygen atom is not adsorbed on the catalyst surface and hydrogenolysis occurs mainly by an S_N2 type of mechanism, leading to an inverted product (Mitsui *et al.*, 1963). In later work, copper and cobalt were found to behave like nickel in hydrogenolysis of benzyl alcohols and to afford products with retained configuration (Mitsui and Kudo, 1965).

These two processes might be expected to have quite different steric requirements, and indeed an example has been reported in which steric hindrance is such that the compound XCIX is inert to Raney nickel, while readily undergoing hydrogenolysis over palladium-on-carbon in acetic acid at 50°C to compound C. The authors think that palladium hydrogenolysis occurred with inversion of configuration by attack of the catalyst on the relatively unhindered α-side of C-6 in a direct displacement process (Brewster and Braden, 1964) (see also page 437).
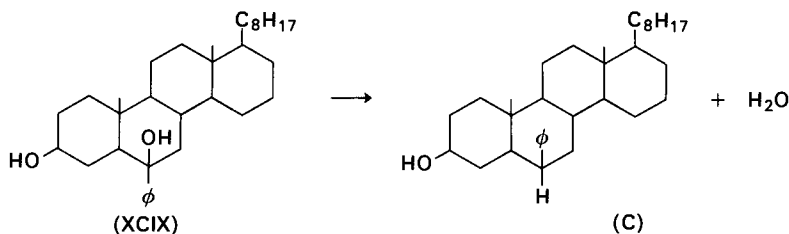
Hydrogenolysis of *cis* and *trans*-α,α'-dimethylstilbene oxide, like other benzyl ethers, undergoes hydrogenolysis with retention of configuration over nickel and with inversion over palladium. The reductions were carried out in ethanol and stopped after absorption of one equivalent of hydrogen.
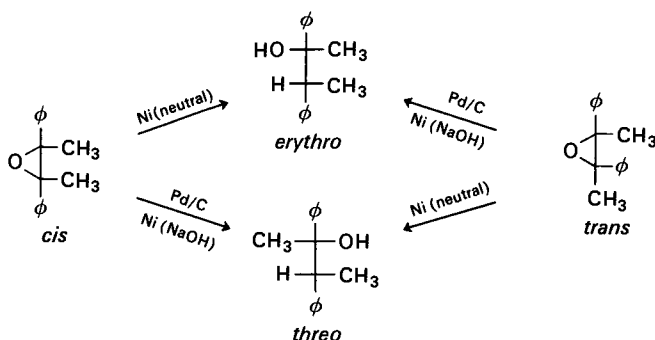
Reduction of the epoxide over Raney nickel in the presence of 0.001 mole of sodium hydroxide per 50 ml solution gave predominantly the inverted alcohol instead of the alcohol with retained configuration. This effect of alkali was not observed in the palladium-catalyzed reductions of these compounds.

The method of preparation of the palladium catalysts had an effect on extent of hydrogenolysis. Hydrogenation of either the cis- or trans-dimethyl-stilbene epoxide over palladium-on-carbon, prepared by evaporating an acid solution of palladium chloride in the presence of carbon, gave 15% of the hydrogenolysis product, 2,3-diphenylbutane, whereas catalysts prepared by alkaline formaldehyde reduction of palladium chloride gave only 2% of 2,3-diphenylbutane. In the presence of dilute sodium hydroxide no diphenyl-butane was formed over the latter catalyst (Mitsui and Nagahisa, 1965). In other work, the method of catalyst preparation had a greater effect on the product. Hydrogenolysis of (−)-menthyl phenylglyoxylate over basic catalysts, such as Raney nickel, platinum oxide, or palladium-on-carbon (prepared by formaldehyde and sodium hydroxide reduction), gave (−)-mandelic acid, whereas palladium chloride-on-carbon or palladium-on-carbon plus hydrochloric acid gave (+)-mandelic acid (Mitsui et al., 1962). Hydrogenolysis of the methyl ester of (−)-γ-hydroxy-γ-phenylvaleric acid over palladium-on-carbon (prepared by hydrogen reduction of palladium chloride) proceeded with high retention of optical activity, which was in-dependent of the palladium concentration on the catalyst. No reduction occurred over a palladium-on-carbon catalyst prepared by alkaline formalde-hyde reduction or with a palladium chloride-on-carbon catalyst when alkali was added. Hydrogenolysis of the more hindered benzoyl derivative, (−)-$C_6H_5CCH_3O(COC_6H_5)CH_2CH_2COOCH_3$, was sensitive to the palladium concentration on the catalyst, the optical activity of the product decreasing sharply with increasing palladium concentration. The authors suggest that the chances of adsorption of the molecule on several sites become greater as the palladium concentration increases and the mechanism shifts from S_N1 at low concentrations of palladium to S_N2 at high concentrations (Senda and Mitsui, 1962).

B. BENZYL GROUPS ATTACHED TO NITROGEN

The benzyl–nitrogen bond is not so easily cleaved as the benzyl–oxygen bond. Compounds such as benzylamine and dibenzylamine (Birkofer, 1942) do not readily undergo hydrogenolysis, whereas the corresponding oxygen compounds are easily cleaved. Nonetheless a wide variety of benzylamines have been reduced successfully under mild conditions (Hartung and Simonoff, 1953).

1. Catalysts

Palladium catalysts are used more than any other in the hydrogenolysis of benzyl–nitrogen compounds (Hartung and Simonoff, 1953). These catalysts are the most active for hydrogenolysis and the least likely to cause concomitant ring saturation. The Pearlman catalyst,* 20% palladium hydroxide-on-carbon, is particularly active for hydrogenolysis of benzyl–nitrogen bonds and has proved successful even where other palladium-on-carbon catalysts have failed (Hiskey and Northrop, 1961). Platinum oxide has frequently been used with success, but in some reductions has proved less satisfactory than palladium (McKennis and Yard, 1958; Hiskey and Northrop, 1961). Other platinum metals do not seem to have been used in these hydrogenolyses.

2. Effect of Structure

The effect of structure on the rate and course of catalytic debenzylation of benzylamines has been investigated in considerable detail. The ease of debenzylation is influenced by both ring and nitrogen substituents. In general, ease of debenzylation increases with increasing substitution on the nitrogen atom, debenzylation of quaternary. amines occurring the most readily (Baltzly and Russell, 1953). Quaternization of the amine may permit selective cleavage of a benzyl–nitrogen bond in the presence of a benzyl–oxygen bond (House et al., 1962; Olin, 1962). A methyl group in the α position of a benzylamine lessens the ease of hydrogenolysis; α phenyl and benzyl groups have less effect (Baltzly and Russell, 1953). A series of competitive debenzylations carried out with ring-substituted benzylamines established the following order of substituents in promoting hydrogenolysis:

$$p\text{-}CH_3O \approx CH_3CONH \approx CH_3COO \approx Cl < NH_3^+ \approx CH_3 < NH_2 < H$$
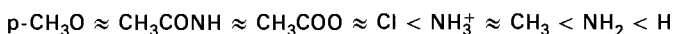
That is, all these substituents, relative to hydrogen, decrease the ease of debenzylation (Baltzly and Russell, 1950; Baltzly and Buck, 1943). The following series of increasing ease of hydrogenolysis of benzyl-like groups in tertiary amines over palladium-on-carbon in ethanol has been established (Dahn et al., 1952):

$$PhCH_2 < p\text{-}PhC_6H_4CH_2 < Ph_2CH < 9\text{-Fluorenyl} < 2\text{- and } 1\text{-}C_{10}H_7CH_2$$
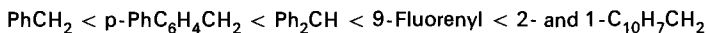
Palladium-on-carbon was the best catalyst for these reductions; Raney nickel and platinum tended to hydrogenate the aromatic rings.

The relative ease of cleavage of various benzylamines may change with the solvent. Hydrogenolysis of N-benzyl-N'-benzhydrylpiperazine (CI) in the presence of hydrochloric acid gave almost exclusively cleavage at A,

* Manufactured by Engelhard Industries, Newark, N.J.

while without acid about 70% of the cleavage occurred at A and 30–40% at B (Baltzly and Russell, 1954):

$$C_6H_5CH_2 \dotplus N \underset{A}{\diagdown} \underset{B}{\diagup} N \dotplus CH(C_6H_5)_2$$

(CI)
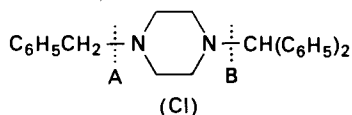
A benzyl group attached to an amidic nitrogen is removed with difficulty. Hydrogenation of ethyl α-benzamido-γ-dibenzylaminobutyrate over 5% palladium-on-carbon in ethanol at 60–70°C gave 1-benzyl-3-benzamido-pyrrolidin-2-one in 80% yield by spontaneous cyclization after removal of one benzyl group. The second N-benzyl group, now part of an amide, resisted further hydrogenation (Sheradsky *et al.*, 1961).

$$\begin{array}{l} N(CH_2C_6H_5)_2 \\ | \\ CH_2CH_2CHCOOC_2H_5 \\ | \\ NHCOC_6H_5 \end{array} \longrightarrow$$
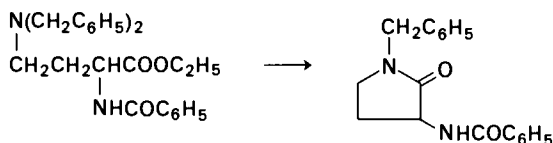
a. Tertiary Benzylamines. Dialkylbenzylamines are readily cleaved (Birkofer, 1942) and the reduction provides a method for synthesis of pure secondary amines (King and Work, 1940). Hydrogenolysis of 27 gm benzyldi-*n*-hexylamine in 30 ml acetic acid over 0.4 gm platinum oxide at 70°C required 6 hours for completion, and afforded di-*n*-hexylamine in quantitative yield. More efficient use of the metal could probably be obtained with supported palladium catalysts. Mixed secondary aliphatic amines may be prepared by a similar reduction. The procedure has been adapted to the preparation of a variety of tertiary amine end products from a single intermediate, through hydrogenolysis of the benzyl group followed by reductive alkylation of the resulting secondary amine (Wright *et al.*, 1961). Many debenzylations are carried out with tertiary amines over palladium and difficulty in the reduction seems to be experienced but rarely.

b. Secondary Benzylamines. Debenzylation of secondary benzylamines does not occur as readily as debenzylation of tertiary amines (Baltzly and Russell, 1953). A number of secondary amines containing one benzyl and one alkyl group appear to be resistant to hydrogenolysis under mild conditions (Buck and Baltzly, 1941; Baltzly and Buck, 1943; Birkofer, 1942). On the other hand, many secondary amines containing an alkyl group carrying a substituent undergo facile hydrogenolysis. 2,3-Diaminosuccinic acid was prepared in 91% yield by hydrogenolysis of 2,3-bis(benzylamino) succinic acid over 10% palladium-on-carbon in acetic acid–hydrochloric acid. (McKennis and Yard, 1958). Hydrogenolysis of the methyl ether of 2-benzylamino-1-phenylethanol (18.9 gm) (CII) in 200 ml ethanol over 3.2 gm 10% palladium-on-carbon afforded the debenzylated product (CIII) in 73%

yield, benzyl-nitrogen cleavage occurring preferentially to benzyl–oxygen cleavage (Kaye and Kogon, 1951):

$$C_6H_5CHCH_2NHCH_2C_6H_5 \longrightarrow C_6H_5CHCH_2NH_2$$
$$\quad\ \ OCH_3 \qquad\qquad\qquad\qquad OCH_3$$
$$\qquad\ \ (CII) \qquad\qquad\qquad\qquad (CIII)$$
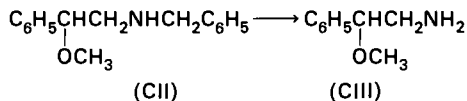
Hydrogenolysis of ethyl-β-benzylaminopropionate hydrochloride over a palladium–platinum-on-carbon in absolute ethanol at 195 psig afforded ethyl β-aminopropionate in nearly quantitative yield (Mattocks and Hartung, 1946). In view of the above examples and others of hydrogenolysis of secondary benzylamines (Zilkha and Golik, 1963; Hartung and Simonoff, 1953), the failure of some simple secondary benzylamines to undergo hydrogenolysis is difficult to understand. Probably all secondary benzylamines would undergo hydrogenolysis over palladium if they were sufficiently pure, or if higher catalyst loadings or more vigorous conditions were used.

c. *Quaternary Benzylammonium Compounds.* Quaternary benzylammonium compounds undergo hydrogenolysis of the benzyl moiety by both catalytic and chemical means (Emde, 1909). Quaternization facilitates hydrogenolysis (Baltzly and Russell, 1953) and provides a method whereby a benzyl–nitrogen bond may be cleaved in preference to a benzyl–oxygen bond. Hydrogenation 342 mg CIV in 25 ml ethanol over 39.4 mg 10% palladium-on-carbon ceased spontaneously after absorption of 0.92 equivalent of hydrogen, and afforded CV in 62% yield after recrystallization. In acetic acid both benzyl groups could be removed. Hydrogenation of 3.11 gm CIV in 20 ml acetic acid over 283 mg 5% palladium-on-carbon afforded CVI in 61% yield after absorption of 2.15 equivalents of hydrogen. Without quaternization, other compounds in this series were preferentially cleaved at the benzyl–oxygen bond (House *et al.*, 1962).
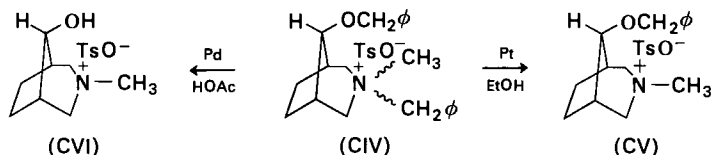
Ammonium salts cannot be used interchangeably, as some anions may have an adverse effect on the catalyst. Tribenzylmethylammonium hydroxide was readily reduced over palladium oxide in ethanol to benzylmethylamine, but the corresponding iodide salt could not be reduced, presumably because of catalyst poisoning by the iodide ion (Birkofer, 1942).

Hydrogenation of benzylphenyldimethylammonium chloride over palladium in ethanol at room temperature and pressure followed a most unusual course. Cyclohexyldimethylamine was obtained from this reduction in 90% yield, providing a very rare example of saturation of an unstrained
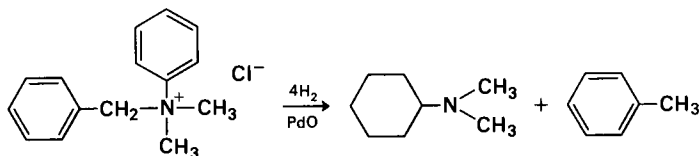
benzene nucleus over palladium under mild conditions (Birkofer, 1942). Probably hydrogenolysis occurred first, affording dimethylaniline, which was then reduced to cyclohexyldimethylamine. Dimethylaniline undergoes a reductive hydrolysis over palladium under mild conditions, whereas quaternary anilinium compounds do not (Kuhn and Haas, 1958).

d. Mannich Bases. Mannich bases of phenols are usually not reduced readily to the corresponding cresols. For instance, hydrogenation of 2-dimethylaminomethyl-4-phenyl-6-chlorophenol over 10% palladium-on-barium sulfate removed only the chlorine, and hydrogenation of 4-nitro-2-dimethylaminomethylphenol reduced only the nitro group (Solodar and Green, 1962). Other workers, by using Mannich bases derived from morpholine, were able to achieve hydrogenolysis where the corresponding dimethylamino derivative was stable. Reduction of 2-chloro-6-morpholinomethyl-4-phenylphenol removed both the amino group and the halogen. Reduction of 2-morpholinomethyl-4-phenylphenol and 3,6-bis(morpholinomethyl)-catechol over 10% palladium-on-carbon in ethanol at 70–80°C and 63–72 psig gave the corresponding methyl derivatives in excellent yield (Fields *et al.*, 1964).

Mannich bases having a nitro group *meta* to the aminomethyl group are reduced readily to the corresponding aminocresols at low pressure under controlled acid conditions (Green and Solodar, 1965). For instance, a mixture of 13.3 gm CVII, 125 ml 95% ethanol, 17.5 ml 3 N hydrochloric acid, and 4 gm 10% palladium-on-barium sulfate, reduced at 50°C and 30 psig, afforded CVIII in 69% yield. Proper control of the acid concentration is necessary for success in this reduction; with no acid present or with more than one equivalent of acid, no debenzylation occurred. The hydrogenolysis was found to go best with about 0.85 equivalent of mineral acid per mole of Mannich base. Hydrogenolysis apparently takes place before the nitro group is completely reduced. When the nitro group was replaced by methoxy, phenyl, or amino, debenzylation did not occur (Solodar and Green, 1962).

(CVII)   (CVIII)
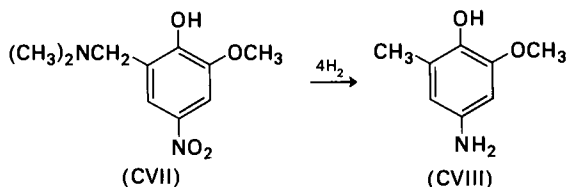
3. Solvent

Debenzylations are carried out usually over palladium in methanol, ethanol, or acetic acid, occasionally with added mineral acid (Hartung and Simonoff, 1953). Interesting use was made of the solvent in controlling selective debenzylation of α-dibenzylamino-γ-butyrolactone (CIX); the same substrate served for preparation of several products. Hydrogenation of 2.8 gm CIX in 100 ml ethanol containing 1 ml concentrated hydrochloride acid over palladium black afforded α-benzylamino-γ-butyrolactone (CX). A similar reduction carried out over 25% palladium chloride-on-carbon gave α-amino-γ-butyrolactone hydrochloride (CXI) in 85% yield. Hydrogenation of 1.4 gm CIX in 50 ml neutral ethanol over 0.7 gm 10% palladium-on-carbon at 60°C afforded the free amino lactone, which dimerized to the diketopiperazine of homoserine (CXII) (70% yield) on further heating. Dimerization was prevented by carrying out the reduction in ethanol–water containing triethylamine. Homoserine (CXIII) was isolated in 75% yield (Sheradsky et al., 1961).
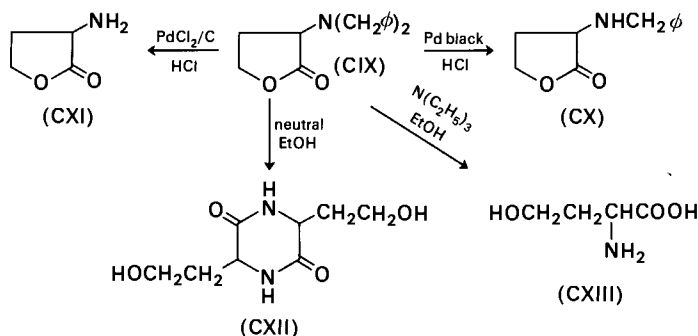
V. HYDROGENOLYSIS OF THE CARBON–CARBON BOND

Hydrogenolysis of the carbon–carbon bond over platinum metal catalysts does not occur under mild conditions, unless the bond has been weakened by some structural feature of the molecule. In effect, hydrogenolysis of the carbon–carbon bond under mild conditions is limited to strained small-ring compounds, and to those compounds where cleavage is facilitated by incipient aromatization or other driving force. Some carbon–carbon bond cleavage may occur competitively with carbon–oxygen bond cleavage during hydrogenation of epoxides (Gawron et al., 1963). A variety of catalysts, including all the platinum metals, have been used to effect carbon–carbon bond cleavage, but in synthetic work palladium or platinum catalysts are the most favored. An interesting and comprehensive review of the mechanism of catalytic hydrogenolysis of small carbon rings has been given by Newham (1963).

A. Unsaturated Cyclopropanes

The cyclopropyl ring does not readily undergo hydrogenolysis under mild conditions in liquid phase, unless activated by adjacent unsaturation or by additional strain. Mixtures may result from hydrogenation of unsaturated cyclopropanes when removal of the unsaturation competes with hydrogenolysis. Reduction of the amino acid, hypoglycin (CXIV), in methanol over platinum oxide resulted in absorption of 1.2 mole of hydrogen, indicating that only 20% of the substrate underwent hydrogenolysis. The hydrogenolysis products were identified as those obtained by cleavage of the bonds adjacent to the unsaturation, i.e., cleavage at a and b; no cleavage occurred at c (deRopp et al., 1958).

(CXIV)
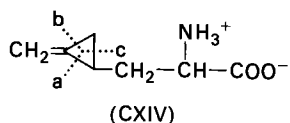
Ullman (1959) examined the course of reduction and the direction of ring opening of a number of substituted vinyl- and alkylidenecyclopropanes. The extent of hydrogenolysis varied widely with the substituents and also somewhat with the catalyst and solvent (Table VI). Ring opening involves preferentially the carbon atom carrying the unsaturation. Two substituents on a single carbon atom strongly facilitate ring cleavage. Hydrogenation of 2-methylenecyclopropane-1,1-dicarboxylic acid gave only n-propylmalonic acid by hydrogenolysis, and a small amount of 2-methylcyclopropane-1,1-dicarboxylic acid. Ullman suggested that hydrogenation of vinyl- and alkylidenecyclopropanes may proceed through a common carbanion intermediate formed by an initial transfer of hydride from the catalyst.

TABLE VI

HYDROGENOLYSIS OF METHYLENECYCLOPROPANE-1,1-DICARBOXYLIC ACID

Catalyst	Solvent	Moles H_2 absorbed
PtO_2	Ethyl acetate	1.86
PtO_2	Methanol	1.92
10% Pd/C	Ethyl acetate	1.58

Some unsaturated cyclopropanes undergo hydrogenolysis so readily that preferential reduction of the unsaturation is difficult, if not impossible. Efforts to achieve saturation of the carbon-carbon double bonds in the allene (CXV) without hydrogenolysis were unavailing; there was no diminution in the rate during absorption of the third mole of hydrogen, and interruption

of the reduction after absorption of two moles gave a complex mixture (Hartzler, 1961):

(CXV)

Similarly, the vinylcyclopropane, α-cyclopropylstyrene, underwent a facile hydrogenation, as if by 1,4-addition, to afford 2-phenylpent-2-ene in quantitative yield. Other reactions also showed vinylcyclopropane to be an active conjugated system when properly activated, as by a phenyl substituent (Sarel and Breuer, 1959).

Hydrogenation of CXVI over palladium-on-carbon in ethanol took an unexpected course, and a mixture of benzoic acid and cyclohexylcarboxylic acid was formed through disproportionation. The saturated acid (CXVII) was formed by hydrogenation over prereduced platinum oxide in ethyl acetate (Meinwald *et al.*, 1963).

Hydrogenation of 7,7-dicyanonorcaradiene over palladium resulted largely in reduction of the cyano groups, but cyclohexylmalonitrile, presumably arising by hydrogenolysis of the cyclopropane ring followed by saturation of the double bonds, was isolated in 10% yield (Ciganek, 1965).

Isomerization Prior to Hydrogenolysis

Quantitative yields of 1,1,4-trimethylcycloheptane (CXXI) have been obtained by hydrogenation of car-3-ene (CXVIII). Hydrogenolysis is believed to be proceded by isomerization to car-2-ene (CXIX) followed by 1,4-addition of hydrogen to give CXX, which may then be isomerized further and reduced to CXXI. The course of this reduction is extraordinarily sensitive to reaction conditions. At 0°C hydrogenation of (+)-car-3-ene over 10% palladium-on-carbon in propionic acid gave 35.5% *cis*-carane (CXXII) and 64.5% trimethylcycloheptane, but as the reaction temperature was raised the percent of hydrogenolysis product steadily increased until it reached 100% at 73°C. Hydrogenation of car-3-ene over platinum-on-carbon at 1500 psig afforded *cis*-carane in 98% yield. If isomerization is a

prerequisite for hydrogenolysis, it is to be expected that less of the hydro-
genolysis product would be formed over platinum, since platinum is not as
active as palladium for double-bond migration (Cocker *et al.*, 1966). The
sequence parallels that found in reduction of CXVI over palladium and
platinum.

(CXXII)   (CXVIII)   (CXIX)   (CXX)   (CXXI)

B. Cyclopropanes with Aromatic Substituents

An aromatic substituent, like other adjacent unsaturation, activates the
cyclopropane ring toward hydrogenolysis. Hydrogenation of phenylcyclo-
propane over palladium black in ethanol gave propylbenzene, by bond
cleavage at the carbon atom bearing the phenyl substituent (Kazanskii
et al., 1958). Hydrogenolysis of 1,2-diphenylcyclopropane occurred over
palladium at 20°C to afford 1,3-diphenylpropane; *trans*-1,2-diphenyl-
cyclopropane reduced about twice as rapidly as the *cis* isomer. On the
other hand, 1,1-diphenylcyclopropane failed to react (Kazanskii *et al.*, 1960),
possibly because the phenyl groups prevented adsorption of the cyclo-
propane ring on the catalyst.

Over catalysts that also saturate the aromatic ring, mixtures result;
hydrogenation of phenylcyclopropane over platinum black afforded a
mixture of propylbenzene, propylcyclohexane, and possibly cyclohexyl-
cyclopropane (Kazanskii *et al.*, 1958). Hydrogenation of 1-methyl-2-α-
furylcyclopropane over 15% palladium-on-carbon at 150°C gave 2-butyl-
tetrahydrofuran in 95% yield, by cleavage of the carbon atoms bearing the
substituents. Similarly hydrogenation of CXXIII gave CXXIV (Shuikin
et al., 1963).

(CXXIII)   (CXXIV)
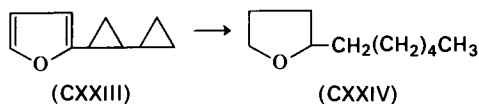
C. Cyclopropenes

Cyclopropenes may be reduced to the corresponding cyclopropanes if
substituents promoting hydrogenolysis of the ring are absent (Carter and
Frampton, 1964). Hydrogenation of 3,3-dimethylcyclopropene in ethanol

over 5% palladium-on-carbon at 0°C afforded 1,1-dimethylcyclopropane in 95% yield. Hydrogenation of 1,3,3-trimethylcyclopropene under the same conditions afforded three parts of 1,1,2-trimethylcyclopropane and one part of an unidentified hydrogenolysis product (Closs and Closs, 1963).

Diphenylcyclopropenone could not be reduced to the corresponding cyclopropane or cyclopropanol. Hydrogenation over platinum oxide in ethanol afforded, after absorption of two equivalents of hydrogen, only dibenzyl ketone. When the reduction was stopped after one equivalent had been absorbed, only starting material and dibenzyl ketone were found; apparently diphenylcyclopropanone, if formed at all, undergoes reduction more easily than the starting material (Breslow et al., 1965).
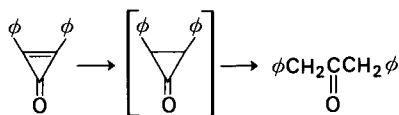
D. Cyclobutanes

Cyclobutanes are reduced less readily than cyclopropanes, reflecting the higher carbon–carbon bond energies (Newham, 1963). As with cyclopropanes, hydrogenolysis of cyclobutanes is facilitated by adjacent unsaturation, by aromatic substituents, and by additional ring strain. Under conditions in which benzocyclobutene was inert or slowly reduced to bicyclo[4.2.0]-octane (Cava and Pohlke, 1963), 1,2-diphenylbenzocyclobutene (CXXV) underwent facile hydrogenolysis to CXXVI (Jensen and Coleman, 1958).

(CXXV)   (CXXVI)
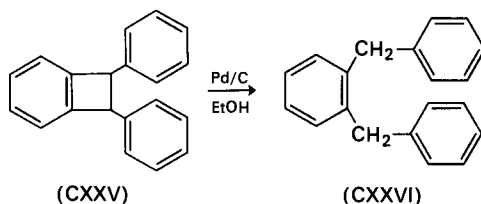
Usually hydrogenolysis of cyclobutane rings requires elevated temperatures and/or pressures. Hydrogenolysis of 1,2-dicyanocyclobutane over rhodium-on-alumina, among other catalysts, at 325°C with a contact time of 1–1.5 seconds gave adiponitrile in 27% yield (Schreyer, 1963). Hydrogenolysis of 3-ethoxy-2,2-dimethylcyclobutanone over 5% palladium-on-carbon at 75°C and 1500 psig gave 3-ethoxy-2,2-dimethylbutyraldehyde.
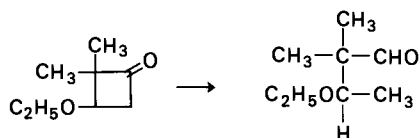
The reduction is of interest, in that hydrogenolysis occurred in preference to reduction of either the ketone or aldehyde function (Hasek *et al.*, 1964).

Hydrogenolysis of a carbon–carbon bond was used to prepare 10α-steroids, especially in the androstane and pregnane series, by reduction over platinum oxide, ruthenium oxide, or 10% palladium-on-carbon at elevated pressures and temperatures of 60–170°C (Cross, 1964).

X = —OH, = O   Y = —OH
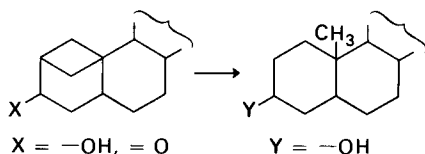
Strained Rings

The ease of hydrogenolysis of cyclobutanes increases with ring strain, which in certain compounds may be very large. The heat liberated in hydrogenolysis of bicyclopentane to cyclopentane was 28 kcal greater than the heat liberated by hydrogenation of isomeric cyclopentene (Seebach, 1965). Hydrogenolysis of CXXVII over palladium-on-carbon in dioxane afforded CXXVIII in 88% yield, whereas under the same conditions benzocyclobutene afforded bicyclo[4.2.0]octane (Cava and Pohlke, 1963).

(CXXVII)   (CXXVIII)
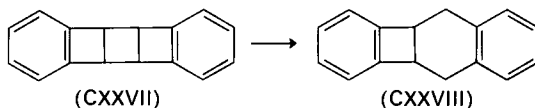
Bicyclobutanes readily undergo hydrogenolysis. Hydrogenation of 2,4-dicarbomethoxybicyclobutane over platinum oxide gave a mixture of *cis*-1,3-dicarbomethoxycyclobutane, dimethyl adipate, and dimethyl α-methylglutarate in a ratio of 15:1:21 (Vellturo and Griffin, 1965). Hydrogenation of ethyl bicyclo[1.1.0]butane-1-carboxylate over platinum gave, after absorption of two moles of hydrogen, ethyl 2-methylbutyrate (Wiberg and Ciula, 1959). Experimental details of the hydrogenation of these bicyclobutane systems were not given, but one gains the impression from comparison with the results of Ullman (1959) that hydrogenolysis occurred too readily to permit a moderately stable cyclopropane intermediate, as has been suggested.

An unusual example of selective hydrogenolysis in a strained hydrocarbon has been reported by Lemal and Shim (1964). Hydrogenation of the hydrocarbon CXXIX (R = H) over 30% palladium-on-carbon in β-ethoxyethanol gave, after absorption of two moles of hydrogen, predominantly methylcyclopentane. When the reduction was carried out over 10% palladium-on-carbon in diglyme and interrupted after absorption of one mole of hydrogen, the product was a mixture of starting material, methylcyclopentane,

bicyclo[2.1.1]hexane, and 1-methylcyclopentene. The authors concluded that scission of the four-membered ring in this substrate was apparently much more rapid than that of the three-membered ring. They pointed out that in the absence of activating functional groups such a preference was without precedent. On the other hand, hydrogenolysis of CXXX (R = COOCH$_3$) gave carboalkoxymethylcyclopentane through preferential cleavage of the three-membered ring (Meinwald et al., 1963).

(CXXIX) R = H
(CXXX) R = —COOCH$_3$
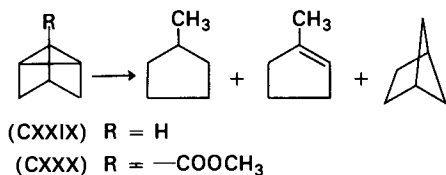
E. Aromatization

Hydrogenolysis of a carbon–carbon bond occurs with particular ease when one of the resulting fragments is converted to an aromatic system in the process. Hydrogenation of CXXXI over platinum oxide afforded CXXXII in good yield (Baird and Winstein, 1957).
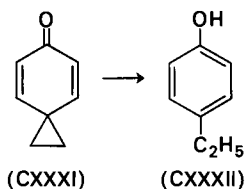
(CXXXI)   (CXXXII)

Lupulone (CXXXIII) readily underwent carbon–carbon bond cleavage over a palladium chloride catalyst, giving a phloroglucinol (CXXXIV) and isopentane. On the other hand, reduction over 5% palladium-on-carbon or over platinum oxide gave hexahydrolupulone derived by saturation of the three exocyclic olefinic bonds. The differences in the catalysts is not due to the presence of hydrochloric acid produced in reduction of palladium chloride; when hydrochloric acid was added to palladium-on-carbon

(CXXXIII)   (CXXXIV)
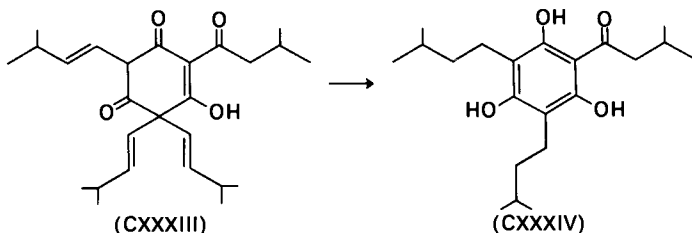
prior to reduction, hexahydrolupulone was still formed (Carson, 1951). (Hydrogenolysis of a similar compound, humulone, is discussed in the chapter on hydrogenation of ketones, page 273.)

F. BENZYL AND PHENYL CARBON–CARBON BONDS

Benzyl carbon–carbon bonds are not easily cleaved under mild conditions, unless the bond is part of a strained system, as noted earlier, or is further weakened by other structural features. The dimer (CXXXV), formed by oxidation of CXXXVI with ferricyanide ion, was readily reduced to CXXXVI over 5% platinum oxide-on-carbon in dioxane at 50 psig and room temperature (Beringer *et al.*, 1963).
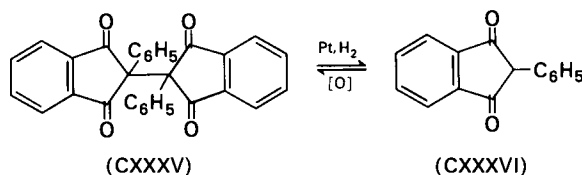
(CXXXV)   (CXXXVI)

Cleavage of the carbon–carbon bond in CXXXV might have been facilitated by adjacent ketonic functions as well as by two phenyl groups. A facile cleavage of the tetraketone (CXXXVII) occurred over colloidal palladium in methanol at ambient conditions to give CXXXVIII. The 5-allyl and isoamylene derivatives, on the other hand, did not undergo hydrogenolysis but gave instead the corresponding 5-propyl and 5-isoamyl compounds (Murin and Riedl, 1959).

(CXXXVIII)

(CXXXVII)
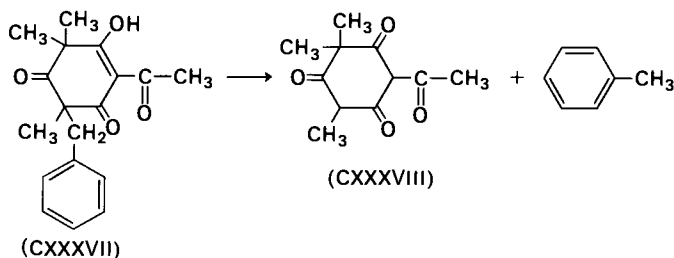
Hydrogenation of CXXXIX over platinum oxide in ethanol–hydrochloric acid or over palladium chloride gave a mixture of CXL, CXLI, and CXLII, the last two compounds being formed by cleavage of a carbon–carbon bond. The double bond is necessary for carbon–carbon bond cleavage to occur, for further reduction of CXL gave only the corresponding decahydroquinoline (Leonard and Foster, 1952). The authors seem disinclined to view

this carbon–carbon bond cleavage under mild conditions as a normal hydrogenolysis reaction.
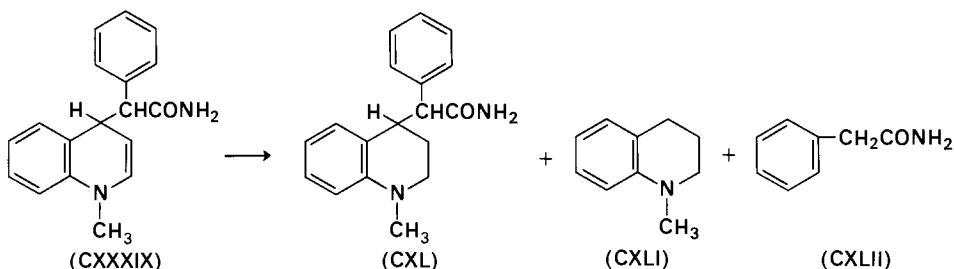
An interesting dephenylation occurred during hydrogenation of 5-(2'-piperidinylmethyl)-5-phenylbarbituric acid hydrochloride over platinum oxide in acetic acid at 50°C:
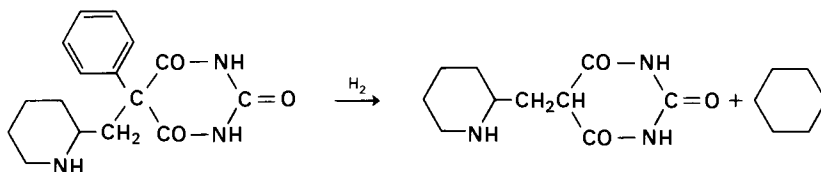
Cleavage of the carbon–carbon bond precedes ring saturation; the corresponding cyclohexyl derivative was unchanged under the conditions of the reaction. The author (Gittos, 1965) suggested that dephenylation involves a cyclic intermediate formed as a result of intramolecular interaction between the 4- or 6-carbonyl group and the piperidinium ion. The process was considered analogous to the facile hydrogenolysis of carbon–carbon bonds in 2-nitro-3-alkylamino propionic ester hydrochlorides over platinum oxide in ethanol (Dornow et al., 1954).

$$RCH\!-\!CH\!-\!COOC_2H_5 \longrightarrow RCH_2NHR'HCl + H_2NCH_2COOC_2H_5$$
$$\quad\ |\qquad |$$
$$\ \ NHR'\ \ NO_2$$
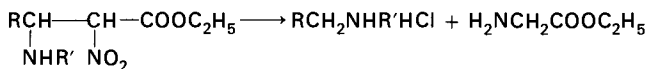
VI. HYDROGENOLYSIS OF THE CARBON–OXYGEN BOND

Facile hydrogenolysis of the carbon–oxygen single bond may occur when the bond is activated as in vinyl-, allyl-, and benzyl-oxygen compounds, phenols, phenyl ethers (Entel et al., 1951; Tomita and Tani, 1944), and phenyl esters. Hydrogenolysis may also occur when there is a tendency for alkene formation by elimination, as in certain bromo esters (Denton et al., 1964) or ketals (Howard and Brown, 1961; Verzele et al., 1963) or in reduction of tertiary alcohols or esters in acid solution (Peterson and Casey, 1964).

(Reductions of all these types have been discussed in other sections.) Hydrogenolysis also occurs when the carbon–oxygen bond is weakened by ring strain, as in epoxides.

Hydrogenolysis of the carbon–oxygen double bond occurs in varying degrees in certain anhydrides, aldehydes, imides (McAlees and McCrindle, 1965), esters, keto esters, ketones, and diketones (discussed in other appropriate sections). Loss of carbonyl oxygen may or may not proceed through an intermediate hydroxy compound, depending on the substrate. The corresponding hydroxy compound may be stable to further reduction, so that hydrogenation affords a mixture of hydroxy and deoxy compounds in proportions that depend on the substrate, solvent, and catalyst. Table VII shows the percent of hydrogenation and hydrogenolysis products formed

TABLE VII

HYDROGENATION OF 2-ACETYLBUTYROLACTONE[a]

Catalyst	Percent 2-ethylbutyrolactone	Percent hydroxylactone	
		Isomer A	Isomer B
5% Rh/C	63.0	12.0	25.0
5% Pt/C	39.4	42.4	18.2
5% Pd/C	5.3	31.4	63.3
5% Ru/C	0	40.0	60.0
5% Ir/C	0	56.4	43.6

[a] Hydrogenations were carried out in water solvent at room temperature and pressure.

on hydrogenation of acetylbutyrolactone over five platinum metal catalysts. The catalysts also had a decisive influence on the ratio of diastereoisomeric hydroxy esters arising through formation of a second asymmetric carbon atom. Under the conditions of the reaction, the hydroxy esters could not be converted to 2-ethylbutyrolactone and hence were not intermediates (Rylander and Starrick, 1966).
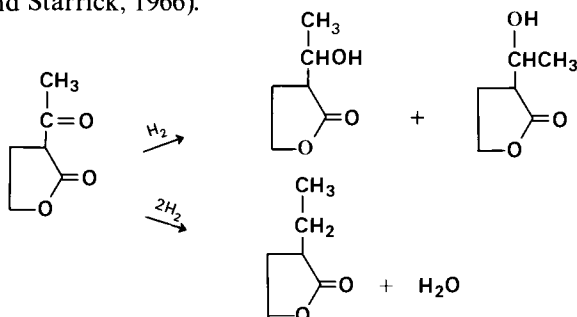
EPOXIDES

Epoxides, with a few exceptions (Berson and Suzuki, 1958), readily undergo hydrogenolysis over platinum metal catalysts. The major product is usually an alcohol or mixture of alcohols resulting from cleavage of a carbon–oxygen bond; other products may arise by cleavage of the carbon–carbon bond and by loss of the oxygen function. The products of reduction may to some extent be anticipated from the structure of the substrate, but both solvent and catalyst also influence the course of reduction.

1. *Solvent*

Hydrogenolysis of epoxides over platinum metal catalysts is usually, but not always, acid-catalyzed. Cyclohexene oxide, for instance, is reduced at a satisfactory rate over platinum in acetic acid. In ethyl acetate the rate is much slower, but is increased sharply by addition of traces of strong acid. No reduction occurs in dioxane, with or without acid present; dioxane, a relatively basic solvent, is known to act as a proton buffer (McQuillin and Ord, 1959). On the other hand, hydrogenolysis of cis-epoxysuccinic acid over 10% palladium-on-carbon is strongly inhibited by acid and accelerated by alkali (Gawron et al., 1963). The direction of ring opening is determined by the solvent as well as by the substrate structure. McQuillin and Ord (1959) have pointed out that acids can have both an accelerating and an orienting effect in the hydrogenolysis of epoxides. For instance, in acetic acid 4,5-epoxycoprostan-3α-ol yields cholestane-3α,4β-diol, but in alcohol coprostane-3α,5β-diol is formed and with difficulty. They have noted that, as a rule, the major product from catalytic hydrogenolysis of steroid oxides is the axial alcohol. Hydrogenolysis of epoxides in acid solution is believed to occur via the conjugate acid with the epoxide ring opening in the sense that will produce the most stable carbonium ion. The direction of opening of terminal epoxides, specifically 1,2-epoxydecane, over Raney nickel was shown to be markedly changed by the presence of trace amounts of base. Without base, mainly 1-decanol resulted; in the presence of small amounts of sodium hydroxide, mainly 2-decanol was formed (Newman et al., 1949). Primary aliphatic alcohols containing little or no secondary alcohol have been obtained by hydrogenation of terminal epoxides over several base metal catalysts, and also over colloidal osmium in acetone at 150°C and 1000 psig (Stein and Rutzen, 1962).

If water is present in the solvent, the hydrogenation product may be a mixture of alcohol and glycol. Hydrogenation of ethylene oxide in ethanol over palladium-on-calcium carbonate gave 91% ethanol and 9% glycol; over nickel-on-silica the product was 80% ethanol and 20% glycol (Ushakov and Mikhailov, 1937).

2. Direction of Ring Opening

The factors controlling the direction of epoxide ring opening are various. The ring may open at the weakest bond, or at the carbon with the fewest substituents (Stavely, 1942), or at the carbon atom with the least steric hindrance, or in acid solution so as to afford the most stable carbonium ion. Hydrogenation of 1-methylcyclohexane oxide over platinum oxide in ethyl acetate containing perchloric acid or over palladium-on-carbon in acetic acid afforded cis- and trans-2-methylcyclohexanol in about equal amounts. No trace of 1-methylcyclohexanol was detected (McQuillin and Ord, 1959). In neutral solution, a nonactivated epoxide may open at the carbon bearing the fewest substituents. The diepoxide (CXLIII), derived from fumagillin, on hydrogenolysis over platinum oxide in ethanol afforded CXLIV by ring opening at the least substituted of the four carbon–oxygen bonds (Ross et al.,

(CXLIII)   (CXLIV)

1956). A highly selective ring opening at the least hindered carbon atom was obtained in hydrogenolysis of CXLV over platinum oxide in ethanol. After hydrogenation and subsequent hydrolysis, the 1,3,4-trihydroxy compound (CXLVI) was obtained in 92 % yield. None of the 5-hydroxy isomer was found (Prostenik et al., 1965).

(CXLV)   (CXLVI)

Epoxides with an adjacent aromatic system often open cleanly at the benzyl–oxygen bond (Whitmore and Gebhart, 1942; Witkop and Foltz, 1957). Hydrogenolysis of styrene oxide gave exclusively β-phenylethyl alcohol regardless of the presence or absence of base (Newman et al., 1949). Similarly, hydrogenolysis of 6α,7α-epoxytotaryl acetate over platinum oxide

in tetrahydrofuran afforded the alcohol derived by cleavage of the benzyl–oxygen bond (Adegoke *et al.*, 1965). Substituents on the aromatic ring may, however, alter the course of reduction to a marked degree, as illustrated by the hydrogenation of various substituted styrene oxides over platinum oxide in ethanol (Park and Fuchs, 1957).

R = p-CH$_3$	0%	100%
R = m-OCH$_3$	12%	88%
R = p-Br	18%	82%
R = 3,4-di-Cl	65%	35%

Epoxides with one carbon–oxygen bond in an allylic position open easily at that bond. Reduction of butadiene oxide over either colloidal palladium or palladium-on-calcium carbonate gave *n*-butanol in good yield. Crotyl alcohol was an intermediate in the reduction, indicating a 1,4-addition of the initial hydrogen. The authors suggested that the primary intermediate was an oxonium salt, formed by either a proton or the catalyst surface (Aizikovich *et al.*, 1958). Chloroprene oxide also gave butanol (Aizikovich and Petrov, 1958).

$$CH_2=CH-CH-CH_2 \longrightarrow [CH_3-CH=CH-CH_2OH] \longrightarrow C_4H_9OH$$

Each bond of an epoxide may undergo hydrogenolysis. Reduction of *cis*-epoxysuccinic acid in water over 10% palladium-on-carbon gave succinic acid, diglycolic acid, and malic acid in molar ratios of 1:2:5. This distribution changes with the pH of the reduction medium; formation of diglycolic acid and succinic acid is favored by increasing acidity.

$$O\begin{matrix}CHCOOH\\|\\CHCOOH\end{matrix} \longrightarrow \begin{matrix}CH_2COOH\\|\\CH_2COOH\end{matrix} + (HOCOCH_2)_2O + \begin{matrix}HOCHCOOH\\|\\CH_2COOH\end{matrix}$$

Reduction of *cis*-epoxysuccinic acid with deuterium afforded *threo*-3-deuterio-DL-malic acid, and reduction of *trans*-epoxysuccinic acid afforded *erythro*-3-deuterio-DL-malic acid. In both cases ring opening occurred with inversion. Some deuterium was found on the methine carbon of the mono-deuterio-DL-malic acid obtained from hydrogenolysis of the *cis*-epoxide, suggesting that some malic acid may have arisen by a different pathway than direct opening of the ring. Conceivably some rearrangement of the epoxide to a ketone may have preceded hydrogenation. Reduction of

trans-epoxysuccinic acid gave *threo*-2,3-dideuteriosuccinic acid, the deuterium apparently adding in *cis* fashion. Hydrogenolysis of *cis*-epoxysuccinic acid gave a mixture of deuterio isomers as if both *cis* and *trans* addition of deuterium had occurred. Malic acid was shown not to be an intermediate in the formation of succinic acid (Gawron *et al.*, 1963).

3. Epoxides of Fatty Acids

Considerable discussion has appeared in the literature regarding the direction of ring opening of epoxides derived from long-chain acids, esters, and alcohols. It was thought at one time that the reduction of these epoxides was highly selective, but later workers with more refined analytical techniques concluded that the ring opening was substantially random. These later findings are in accord with intuitive expectations, for the elements making the epoxide asymmetric are far removed from the functional group itself.

Hydrogenation of methyl *cis*-9,10-epoxystearate over 5% palladium-on-carbon in acetic acid gave equal amounts of 9- and 10-hydroxystearates, together with smaller amounts of stearate and ketostearate. This work refuted claims of earlier investigators that the 10-hydroxystearate was the predominant product. The ketostearate was shown to be a product of the hydrogenation; the action of acetic acid on the epoxy esters alone produced no ketostearate (Howton and Kaiser, 1964). Reduction of *cis*-9,10-epoxyoctadecanol and *cis*-9,10-epoxyoctadecyl acetate in ethanol over palladium-on-carbon also gave nearly equal proportions of the 9- and 10-hydroxy isomers (Fore and Bickford, 1959). Catalytic hydrogenolysis of *cis*-6,7-epoxyoctadecanoic acid over 10% palladium-on-carbon in ethanol gave nonselectively about equal amounts of the 6- and 7-hydroxyoctadecanoic acids. One reduction was unexpectedly and unusually rapid and gave in addition to the hydroxy acids about 40% of stearic acid. Although reductions were successful over 10% palladium-on-carbon, they failed over Raney nickel, platinum oxide, or palladium-on-calcium carbonate (Fore and Bickford, 1961). One recent selective hydrogenation has been reported. Mainly 14-hydroxydocosanoic acid was obtained by hydrogenation of either *cis*- or *trans*-13,14-epoxydocosanoic acid over palladium in ether (Rubashko, 1964).

The hydrogenolysis of the epoxide of petroselinic acid (*cis*-6-octadecenoic acid) took an unusual course; only stearic acid was formed at ambient conditions over 10% palladium-on-carbon in absolute ethanol. After absorption of one mole of hydrogen, the product was a mixture of unchanged starting material and stearic acid (Pigulevski and Sokolova, 1963).

4. Selective Hydrogenation of Epoxides

The products resulting from hydrogenation of an oxirane containing another reducible function depend largely on the substrate. However, the

course of reduction may also be influenced to some extent by the catalyst. For instance, reduction of the double bond in CXLVII could be achieved with or without hydrogenolysis of the epoxide by proper choice of catalyst. Over platinum oxide only the double bond was reduced; over 10% palladium-on-carbon the double bond was reduced, and the epoxide ring opened at the benzyl carbon–oxygen bond. The trend, if not the extent, of selectivity could have been predicted, i.e., platinum would give minimum, and palladium maximum, hydrogenolysis (Poos and Rosenau, 1963).
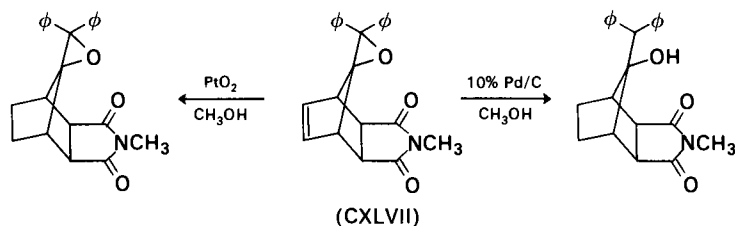
(CXLVII)

Rhodium may prove even more useful than platinum in achieving double bond saturation without epoxide ring hydrogenolysis. The unsaturated compounds CXLVIII were smoothly reduced to CXLIX over rhodium-on-alumina in ethanol, whereas over platinum in ethanol considerable hydrogenolysis occurred, the ring opening in the direction indicated (Tarbell et al., 1961).

(CXLVIII)   (CXLIX)
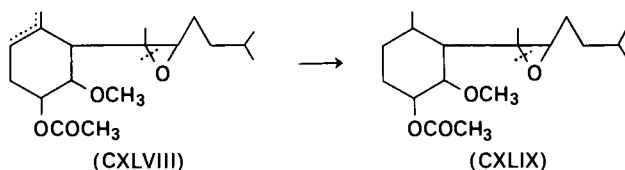
An interesting comparison of catalysts was made in hydrogenation of an epoxy ketone (CL), and again it appears that palladium favors hydrogenolysis of the epoxide ring, platinum its preservation. One might assume from the products that, if hydrogenolysis precedes reduction of the ketone, the carbon–oxygen bond adjacent to the ketone is broken; if ketone reduction precedes hydrogenolysis, the benzyl carbon–oxygen bond is broken (Cromwell and Bambury, 1961). Perhaps the carbon–oxygen bond adjacent to the ketone is opened by 1,4-addition of hydrogen to the oxygen atoms.
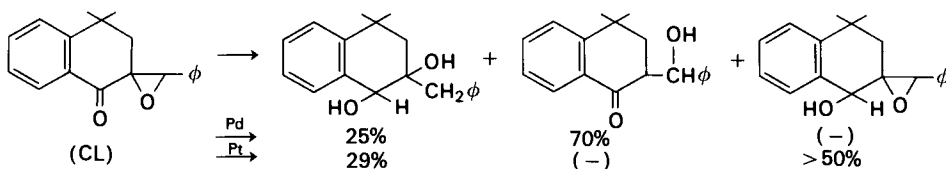
A similar distinction between palladium and platinum was observed in hydrogenation of benzalacetone oxide. Over platinum black or nickel-platinum, reduction of the carbonyl was favored but, over nickel-palladium, benzyl–oxygen hydrogenolysis predominated (Temnikova and Kropachev, 1949). On the other hand, in hydrogenation of benzalacetophenone oxide (Herz, 1952) the initial step was hydrogenolysis of the benzyl–oxygen bond regardless of catalyst (platinum oxide, 5% palladium-on-carbon, or Raney nickel) or solvent (alcohol, ether, ethyl acetate, or acetic acid).

Selective hydrogenation of one carbonyl function in CLI to afford CLII without ring opening can be achieved with platinum oxide catalysts. The substrate must be carefully purified, and relatively large amounts of catalyst were required to bring the reduction to completion. Absolute ethanol was superior to 95% ethanol. A typical reduction was carried out with 20 gm substrate in 300 ml absolute ethanol over 1.4 gm platinum oxide. One equivalent of hydrogen was absorbed in 4 hours. In some experiments the yield of CLII was as high as 95% (Lutz and Wood, 1938).

$$C_9H_{11}COCH-CHCOC_9H_{11} \longrightarrow C_9H_{11}CHCH-CHC-C_9H_{11}$$

$$C_9H_{11} = \text{mesityl}$$
$$\text{(CLI)}$$

$$\text{(CLII)}$$
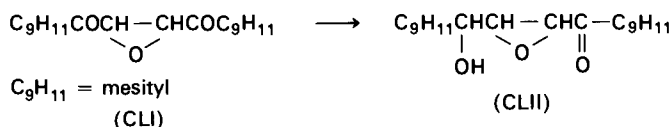
VII. HYDROGENOLYSIS OF THE CARBON–NITROGEN BOND

Hydrogenolysis of the carbon–nitrogen bond occurs more readily than hydrogenolysis of the carbon–carbon bond, and less so than cleavage of the carbon–oxygen bond. Hydrogenolysis of the carbon–nitrogen bonds under mild conditions are limited to those compounds in which the bond is in some way weakened, as in vinyl, allyl, or benzyl compounds, or by other unsaturation, as in α-amino nitriles. Cleavage may occur in those compounds in which a nitrogen moiety may undergo elimination, leaving an easily reduced olefin or imine structure, as in the coupling reactions of nitriles. Hydrogenolysis of the carbon-nitrogen bond occurs readily if the bond is weakened by steric strain. The carbon–nitrogen bond may be cleaved by reductive hydrolysis, as in hydrogenation of N,N -dialkylanilines or oximes. (Most of these reductions have been discussed in other sections.)

AZIRIDINES AND AZIRINES

The aziridine ring is moderately stable to hydrogenation and can itself be prepared by saturation of an azirine ring (Morrow et al., 1965). Hydrogenolysis of the azirine ring may occur before ring saturation. Hydrogenation

of CLIII over 5% palladium-on-carbon in pyridine–acetic anhydride gave a mixture of CLIV and CLV. Over Raney nickel, 2,4-dinitrophenylacetone was obtained in 49% yield, presumably through hydrolysis during work-up of an intermediate imine. The great susceptibility to hydrogenolysis of the carbon–nitrogen single bond of the azirine ring was attributed to ring strain and to the stabilizing effect of the nitro groups upon the transition state of the reduction reaction. The shift of the double bond into conjugation was attributed to enhanced resonance stabilization in CLIV and CLV (Cram Hatch, 1953),
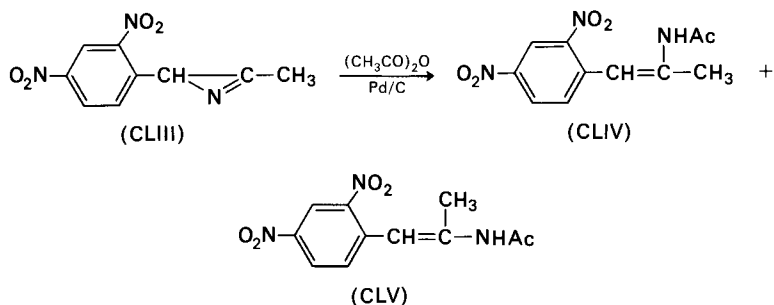
Aziridines can undergo hydrogenolysis as the free base in neutral solution (Wang and Cohen, 1961) or as certain acid salts. Successful reductions have been carried out over palladium (Stevens *et al.*, 1964), platinum, and Raney nickel. No comparison of the relative effectiveness of catalysts has been made.

Direction of Ring Opening

Hydrogenolysis of the aziridine ring occurs primarily at the less hindered carbon–nitrogen bond, except when the more hindered carbon carries unsaturation. Hydrogenation of 2,2-dimethylethyleneimine afforded only *t*-butylamine without isobutylamine (Karabinos and Serijan, 1945; Campbell *et al.*, 1946). Similarly, hydrogenation of 1.0 gm CLVI in 100 ml anhydrous methanol over 0.4 gm platinum oxide afforded CLVII in 70% yield. This cleavage between the quaternary nitrogen and methylene carbon contrasts with alcoholysis, which ruptures the bond between the rings (Leonard
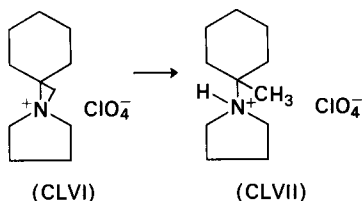
and Jann, 1962). Hydrogenolysis of other compounds similar to CLVI was achieved readily over platinum oxide in anhydrous acetone, major cleavage again occurring between the nitrogen atom and the least hindered carbon (Leonard et al., 1963).

Hydrogenation of 2.5 gm 1-(2-methylene-1-aziridinyl)-3-buten-2-ol in 100 ml absolute ethanol over 0.2 gm platinum oxide led to cleavage between the vinylic carbon and nitrogen atom, instead of, as is usually the case, between the nitrogen and less hindered ring carbon (Bottini et al., 1963):

$$H_2C \diagdown \text{(aziridine ring with N)} \qquad \longrightarrow \qquad CH_3CH_2CH_2NHCH_2\overset{\overset{\displaystyle OH}{|}}{C}HCH_2CH_3$$

with substituent $CH_2\overset{\overset{\displaystyle |}{}}{C}HCH=CH_2$ bearing OH
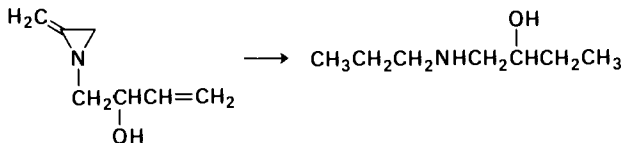
Similarly, hydrogenation of N-(p-toluenesulfonyl)styreneimine over 5% palladium-on-barium sulfate in methanol led to cleavage at the benzylic nitrogen–carbon bond with formation of N-phenethyl-p-toluenesulfonamide (Kharasch and Priestley, 1939).

VIII. HYDROGENOLYSIS OF THE NITROGEN–OXYGEN BOND

Nitrogen–oxygen bonds in general undergo catalytic cleavage with ease, as exemplified by many facile reductions of the nitro, nitroso, hydroxylamine, and oxime functions. It appears that most nitrogen–oxygen bonds, unless severely hindered, are susceptible to hydrogenolysis.

A. AMINE OXIDES

Pyridine oxides are reduced easily to the amine and water over platinum metal catalysts. Palladium-on-carbon is said to be the preferred catalyst for this type of reduction (Bodendorf and Binder, 1954), and is in fact most often used. In certain reductions rhodium may prove more useful. The rates of reduction of pyridine-N-oxide over 5% palladium-, platinum-, rhodium-, and ruthenium-on-carbon in methanol, water, and acetic acid were compared, and in every case rhodium was the most active catalyst. Reduction over rhodium is nonselective, and the pyridine ring is reduced concomitantly with nitrogen–oxygen bond cleavage (Rylander and Rakoncza, 1962). Rhodium is the preferred catalyst when a piperidine is the desired end product.

Katritsky and Monro (1958) examined the reduction of 39 pyridine-1-oxides to the corresponding pyridine over 5% palladium-on-carbon in ethanol. Carbon–carbon double bonds and chlorine tend to be reduced before an N-oxide function, but both 3- and 4-acetylpyridine-1-oxide lost the oxide function before the carbonyl was reduced.

Selectivity depends on the position as well as the nature of the substituent. Hydrogenation of 4-nitropyridine-1-oxide over 5% palladium-on-carbon afforded 4-aminopyridine-1-oxide, whereas 2-nitropyridine-1-oxide afforded only 2-aminopyridine (Brown, 1957). Reduction of 3-nitropyridine-1-oxide over platinum oxide in ethanol afforded 3-aminopyridine (Taylor and Driscoll, 1960). Hydrogenation of 2-benzyloxypyridine-1-oxide over palladium-on-carbon gave 1-hydroxy-2-pyridone (Shaw, 1949; Lott and Shaw, 1949), whereas reduction of the 4-isomer may give either 1-hydroxy-4-pyridone or, if the reduction is continued, 4-pyridone (Katritsky and Monro, 1958).

Amine oxides related to pyridine are more easily reduced than aromatic and aliphatic tertiary amine oxides (Ochiai et al., 1943), but nonetheless aliphatic amine oxides are also reduced readily over palladium-on-carbon. Hydrogenation of CLVIII and CLIX over 5% palladium-on-carbon in ethanol afforded CLX and CLXI in 81% and 85% yields, respectively, with little or no hydrogenolysis of the benzyl alcohol (Stevens and Chang, 1962).

(CLVIII)   R = —CH₃   (CLX)   R = —CH₃
(CLIX)   R = —(CH₂)₅—   (CLXI)   R = —(CH₂)₅—
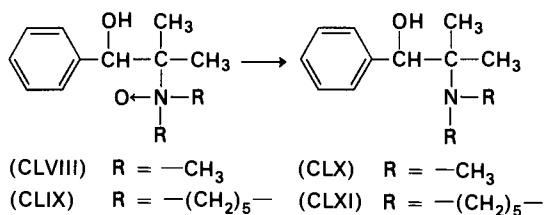
Quantitative yields of diphenylketazine were obtained by hydrogenation of diphenylketazine oxide (1 gm) in 200 ml ethanol over platinum oxide (Lauer and Dyer, 1942).

$$(C_6H_5)_2C{=}N{-}\underset{\underset{O}{\uparrow}}{N}{=}C(C_6H_5)_2 \longrightarrow (C_6H_5)_2C{=}N{-}N{=}C(C_6H_5)_2$$
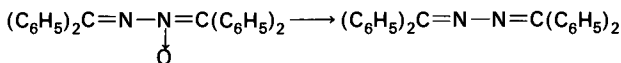
B. HETEROCYCLIC COMPOUNDS

Many heterocyclic compounds containing an oxygen–nitrogen linkage undergo facile hydrogenolysis under mild conditions with ring opening. Palladium or platinum is usually used in these reductions; hydrogenation over other platinum metals does not seem to have been attempted.

Catalytic hydrogenation of 10 gm of the furazan oxide (CLXII) in 100 ml ethyl acetate over 0.1 gm platinum oxide afforded 4-chloro-3-methoxy-1,2-phenylenediamine (CLXIII) (Mallory and Varimbi, 1963).

(CLXII)   (CLXIII)
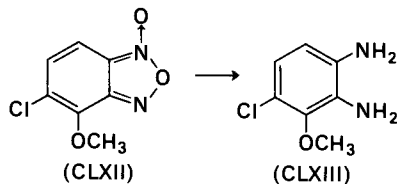
Hydrogenolysis of 3-phenylanthranils offers a convenient route to *o*-aminobenzophenones. Reductions carried out at 40–60°C over 10% palladium-on-carbon in ethyl acetate afford practically pure amino ketones on evaporation of the filtered solution (Walker, 1962).
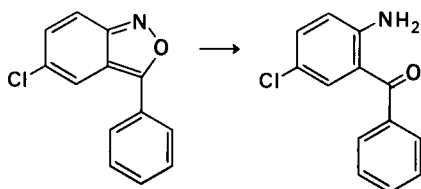
Oxazirans can be differentiated from the isomeric nitrones by the products of their reduction (Schmitz, 1963). Catalytic hydrogenation over platinum of 2-cyclohexyl-3-phenyloxazirane afforded benzylcyclohexylamine, whereas the isomeric nitrone gave the disubstituted hydroxylamine (Horner and Jürgens, 1957).

Isoxazoles

Isoxazoles undergo hydrogenolysis of the ring over platinum metals, with reduction of di- and tetrahydroisoxazole derivatives proceeding more readily than reduction of the aromatic system of isoxazole (Kochetkov and Sokolov, 1963). Styrylisoxazoles show an increased stability to reduction, but nonetheless are cleaved over platinum catalysts (Lampe and Smolinska, 1958). Almost all known examples of catalytic hydrogenation of isoxazole derivatives are accompanied by hydrogenolysis of the ring. Earlier reports (Shaw, 1950, 1951) that hydrogenation over palladium of 3-alkyl-4-amino-methyleneisoxazol-5-ones resulted in saturation of either the endocyclic carbon–nitrogen double bond, or the exocyclic carbon–carbon double bond with retention of the heterocyclic ring, have been questioned (Kochetkov *et al.*, 1959). An exception to the rule is the reduction over palladium of an azo function with preservation of the isoxazole ring (Kochetkov and Sokolov, 1963). Isoxazoline oxides seem to be much more resistant to hydrogenolysis than the corresponding isoxazoline (Kohler and Davis, 1930).

Monoimines resulting from hydrogenolysis of isoxazoles can sometimes be isolated, but usually undergo further transformation (Kochetkov and Sokolov, 1963). Hydrogenation of 3 gm CLXIV in 180 ml dimethylformamide

(CLXIV)   (CLXV)
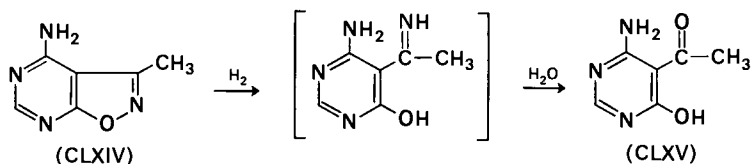
over 0.4 gm 10% palladium-on-carbon afforded CLXV in 91% yield after hydrolysis. The intermediate imine proved too unstable for characterization (Taylor and Garcia, 1964). If hydrogenolysis of isoxazole derivatives is carried out in acetic acid–acetic anhydride, diacetyl derivatives may be obtained directly (Cope and LeBel, 1960).

IX. HYDROGENOLYSIS OF THE OXYGEN–OXYGEN BOND

Peroxides, hydroperoxides, and ozonides are easily cleaved by hydrogen over platinum metal catalysts. Decomposition may occur also in the absence of hydrogen, and platinum metals are often used to destroy excess hydrogen peroxide in synthetic work (Cope and Ciganek, 1963). Ruthenium is by far the most active of the platinum metals for decomposition of concentrated hydrogen peroxide, whereas supported platinum is the most active for decomposition of peroxy acids (Andersen and Romeo, 1964) and hydroperoxides (British Patent 1,009,939).

A. Ozonides

Hydrogenolysis of ozonides to aldehyde and ketones is complex, and acids and other rearrangement products may be formed as well (Bailey, 1958). Better yields are obtained by reduction in reactive solvents, such as methanol, than in nonreactive solvents (Pyrde et al., 1960). Further improvements are obtained by carrying out the reduction in the presence of pyridine (Pryde et al., 1962). In a typical experiment, 20.8 gm methyl oleate in 250 ml absolute methanol and 22.8 gm pyridine were ozonized and, after completion, the reactor was flushed with nitrogen and 0.1 gm 10% palladium-on-carbon added. Hydrogenation, carried out for 100 minutes at room temperature and pressure, afforded methyl azelaaldehydate in 76% yield. On a larger scale the yields were higher.

Some complications of catalytic hydrogenation of ozonides have been described by Thompson (1962). Hydrogenation of CLXVI, derived by ozonolysis of 16.8 gm dihydropyran, over 100 mg platinum oxide in 100 ml methanol afforded 4-formoxybutyraldehyde (CLXVII) in 42% yield, methyl 4-formoxy-butyrate (CLXVIII) in 21% yield, and γ-butyrolactone (CLXIX)

(CLXVI)   (CLXVII)   (CLXVIII)   (CLXIX)
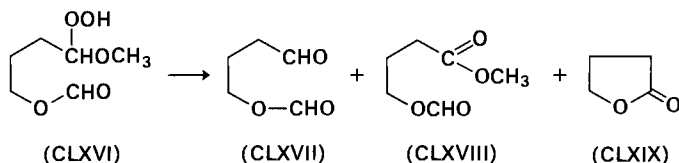
in 9% yield. Reduction with tributyl phosphite, on the other hand, afforded 4-formoxybutyraldehyde in 80% yield.

The ozonide of 2-phenylskatol (CLXX) is remarkably stable. It undergoes hydrogenolysis over palladium black in ethyl acetate to *o*-benzamino-acetophenone (CLXXII), which can also be obtained from CLXX by re-fluxing it in chloroform in the presence of *p*-toluenesulfonic acid. The authors (Witkop and Patrick, 1952) believe that hydrogenolysis of CLXX starts from the tautomer (CLXXI) to form a hemiacetal, which isomerizes easily to *o*-benzaminoacetophenone.

(CLXX)   (CLXXI)   (CLXXII)
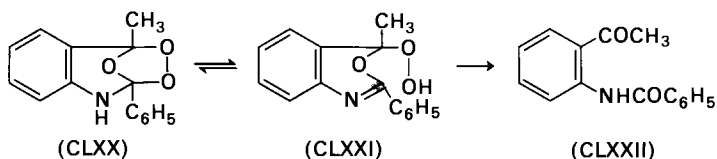
B. PEROXIDES

Hydrogenation of peroxides is usually carried out over palladium or platinum and yields alcohols or glycols, often in excellent yields. The reduction proceeds easily, and modified catalysts or catalyst inhibitors may be used to prevent reduction of other functions or to prevent hydrogenolysis of the hydroxyl. Hydrogenation of styrene peroxide over palladium or platinum is best carried out in the presence of an amine; phenylethylene glycol is obtained in appreciably higher yields when an amine is present (Russell and Mayo, 1957). Palladium-on-calcium carbonate inhibited by lead (Lindlar catalyst) is useful for hydrogenolysis of peroxides, when olefin saturation is to be prevented (Laubach, 1957; Agnello *et al.*, 1956).

Oxidation of olefins to peroxides followed by hydrogenolysis provides a convenient synthesis of glycols (Agnello *et al.*, 1956; Cope *et al.*, 1957). Autoxidation of 2,5-dimethyl-2,4-hexadiene affords in good yield the corresponding *trans*-1,4-polyperoxide, the only detectable product. On reduction over 10% palladium-on-carbon in tetrahydrofuran at 150 psig., the carbon–carbon bonds were reduced and the oxygen–oxygen bond cleaved to give nearly quantitative yields of 2,5-dimethylhexane-2,5-diol. Hydrogenolysis of the peroxide linkage without olefin saturation was achieved by base-catalyzed reduction with an aromatic thiol (Griesbaum *et al.*, 1964).
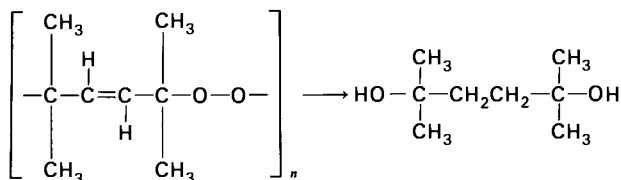
Catalytic hydrogenation of 3 gm of the peroxide (CLXXIII) in 300 ml absolute ethanol over 200 mg platinum oxide rapidly absorbed two equivalents of hydrogen and afforded the oxazole (CLXXIV) in 82% yield. If the reduction were carried out until three equivalents were absorbed, the monohydroxy compound (CLXXV) was obtained (McKay *et al.*, 1964). Presumably the oxazole arises through a glycol intermediate.

(CLXXV)   (CLXXIII)   (CLXXIV)
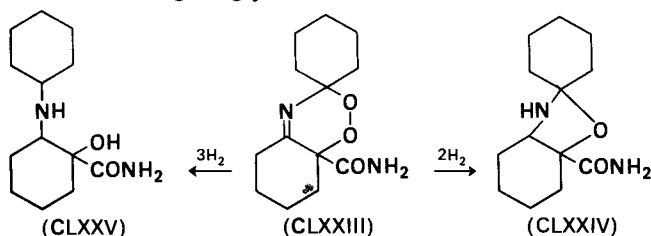
C. HYDROPEROXIDES

Hydroperoxides can be easily reduced to the corresponding alcohols over palladium or platinum catalysts (Japanese Patent 26,961/64; Lythgoe and Trippett, 1959; Fuson and Jackson, 1950; Fuchs, 1960; von Wittenau, 1964; Stevens and Gasser, 1957). Hydroperoxides obtained by oxidation of an olefin may be selectively reduced to an unsaturated alcohol over inhibited palladium catalysts. Hydrogenation of 4.1 gm cyclohexenyl hydroperoxide in 20 ml ethanol containing 0.02 gm quinoline over a palladium catalyst inhibited by lead afforded cyclohexenol in 84% yield (German Patent 1,205,965). Similar inhibited catalysts are useful for selective hydrogenation of hydroperoxides in the presence of peroxides (Belgian Patent 626661).

Witkop and Patrick (1951) prepared 11-hydroxytetrahydrocarbazolenine (CLXXVII) by catalytic oxidation* of tetrahydrocarbazole (CLXXVI) and subsequent hydrogenation of the intermediate hydroperoxide. The same platinum catalyst was used for both reactions. Tetrahydrocarbazole, 1.0 gm in 10 ml ethyl acetate containing 200 mg reduced platinum catalyst, was stirred under oxygen for 4 hours. An induction period always occurred unless the catalyst was shaken separately with oxygen before the oxidation was begun. Care was taken that no catalyst was splashed up on the walls of

(CLXXVI)   (CLXXVII)
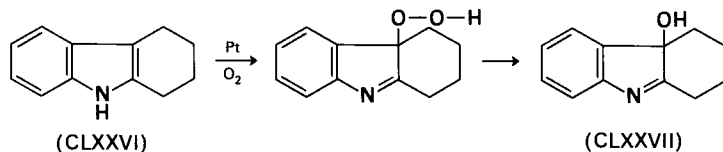
* A review of selective catalytic oxidations over platinum metal catalysts has been given by Heyns and Paulsen (1963).

the flask in order to prevent explosive oxidation. The reaction was discontinued when 92% of the theoretical oxygen had been absorbed, and the system evacuated and refilled with hydrogen. Theoretical hydrogen was rapidly absorbed and CLXXVII obtained in 75% yield.

X. HYDROGENOLYSIS OF THE NITROGEN–NITROGEN BOND

Hydrazines (Cram and Bradshaw, 1963; Daves *et al.*, 1962; Overberger *et al.*, 1955) and compounds that on hydrogenation afford hydrazines all undergo nitrogen–nitrogen bond cleavage over platinum metal catalysts. Palladium, platinum, and rhodium (Overberger and Marks, 1955) have been used successfully in these reductions, but only very limited studies have been made of the relative effectiveness of platinum metal catalysts in nitrogen–nitrogen bond hydrogenolysis. In general, the rate of saturation of azines, hydrazones, azo compounds, and nitrosoamines is greater than the rate of hydrogenolysis, so that intermediate hydrazines may be isolated, usually in good yield. (Reduction of these functions with emphasis on minimum hydrogenolysis is discussed in other chapters.)

A. AZO COMPOUNDS

Hydrogenation of azo compounds usually proceeds stepwise with formation of hydrazo derivatives followed by, if the reduction is continued, hydrogenolysis of the nitrogen–nitrogen bond. Skita (1912) obtained hydrazobenzene by reduction of azobenzene over colloidal palladium in 5 minutes and aniline in 270 minutes. Even the highly strained 3,3-pentamethylenediazirine afforded 3,3-pentamethylenediaziridine in 13% yield, after absorption of one mole of hydrogen. Complete reduction resulted in cyclohexylamine and ammonia (Schmitz and Ohme, 1961).
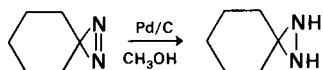
Diazo coupling with an activated nucleus, followed by catalytic hydrogenolysis, provides a convenient sequence for introduction of an amino function. 2-Methyl-4,5,6-trimethoxyaniline was prepared in this way by coupling 3,4,5-trimethoxytoluene with a diazonium salt of *p*-nitroaniline and reducing the resulting azo compound over palladium-on-carbon (British Patent 889, 704). 2-Amino-5-hydroxypyridine (CLXXIX), isolated as a benzoyl derivative in 76% yield, was similarly prepared. A solution of 25 gm CLXXVIII in 150 ml acetic acid was shaken with 0.3 gm 10% palladium-on-

carbon catalyst at 45 psig. Theoretical hydrogen was absorbed in 30 minutes (Moore and Marascia, 1959).

(CLXXVIII) → (CLXXIX)
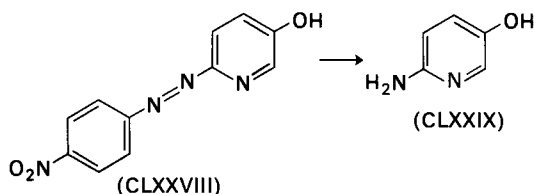
Hydrogenation of CLXXX in formic acid resulted in the monoformyl derivative of CLXXXI. A solution of 20 gm CLXXX in 100 ml 90% formic acid, hydrogenated over 1 gm 10% palladium-on-carbon at 3 atm until absorption ceased in 45 minutes, afforded CLXXXI in 89% yield (Taylor *et al.*, 1958).
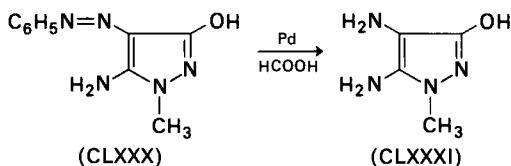
(CLXXX) → (CLXXXI)

A synthesis of 1-phenyl-2-amino-1,3-propanediol (CLXXXIII) involved hydrogenation of CLXXXII over platinum oxide. Nearly quantitative yields of *erythro*-CLXXXIII were obtained on hydrogenation of 8.48 gm CLXXXII in 90 ml acetic acid over 0.2 gm prereduced platinum oxide.* Six equivalents of hydrogen were absorbed in 24 hours. It is interesting that five equivalents were consumed in reduction of the azo moiety to ammonia and cyclohexylamine, whereas little or no reduction of the other phenyl ring occurred (Bodendorf and Wössner, 1959).

(CLXXXII) → (CLXXXIII)
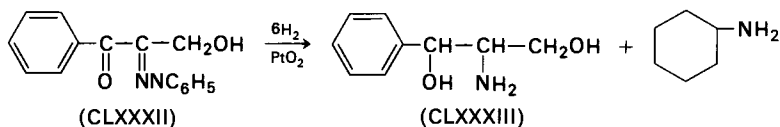
The absolute and relative rates of hydrogenation and of hydrogenolysis of the azo linkage depend on the substrate, catalyst, and solvent. Table VIII gives rates for the saturation (first mole of hydrogen absorbed) and the hydrogenolysis (second mole of hydrogen absorbed) of azobenzene in ethanol and in acetic acid over three platinum metal catalysts. In contrast to reduction of azobenzene, hydrogenation of *p*-phenylazobenzene proceeds at a constant rate until two equivalents of hydrogen are absorbed, and then the absorption

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* *threo*-CLXXXIII may be made by stirring *threo*-1-phenyl-2-nitropropane-1,3-diol with aqueous formic acid over platinum oxide or palladium-on-carbon (Pearlman, 1966).

TABLE VIII

HYDROGENATION OF AZOBENZENE[a]

Catalyst	Rate (ml H_2 absorbed/minute/100 mg catalyst)			
	Ethanol solvent		Acetic acid solvent	
	1st mole H_2	2nd mole H_2	1st mole H_2	2nd mole H_2
5% Pd/C	11	2	100	45
5% Pt/C	19	1	47	5
5% Rh/C	15	>1	30	3

[a] Experiments were carried out with 100 mg catalyst, 50 ml solvent, and 2.0 gm azobenzene at room temperature and pressure. Each rate curve consisted of two substantially straight-line portions with an inflection at one mole of hydrogen absorbed (Rylander and Karpenko, 1960).

ceases abruptly (Table IX). The relative activity of the catalysts also changes with the substrate and solvent. Palladium would seem to be generally the best catalyst for hydrogenolysis of the azo linkage and is in fact often used. Platinum oxide has been used for both hydrogenation (Andrews and Lowy, 1934) and hydrogenolysis of the azo linkage (Stevens and Freeman, 1964) with moderate success.

TABLE IX

HYDROGENATION OF p-PHENYLAZOANILINE[a]

Catalyst	Rate (ml H_2 absorbed/minute/100 mg catalyst)	
	1st mole	2nd mole
5% Pd/C	95	95
5% Pt/C	30	30
5% Rh/C	40	40

[a] Each reduction was carried out with 100 mg catalyst, 50 ml acetic acid, and 2.0 gm p-phenyl-azobenzene at room temperature and pressure. Selectivity at half-hydrogenation was not measured in these experiments.

B. DIAZO COMPOUNDS

The hydrogenation of diazo compounds may be complex and afford a variety of products that depend on the substrate and the reaction environment. Pyrazines, amino ketones, diketones, amino alcohols, chloroketones, and hydrazones have all been isolated from hydrogenation of diazo ketones over palladium or platinum catalysts (Birkofer, 1947). Nonetheless by

suitable choice of conditions the reduction can be made to go reasonably cleanly. Catalytic hydrogenolysis proved especially advantageous in the reduction of methyl benzoyldiazoacetate (CLXXXIV), a compound reduced unsatisfactorily with a variety of chemical reducing agents. Hydrogenation of 10 gm CLXXXIV was carried out with 70 ml glacial acetic acid and 0.5 gm 5% palladium-on-carbon, to which 30 ml water was added immediately before hydrogenation was begun. Theoretical hydrogen was absorbed in 5 hours and allophenylserine methyl ester (CLXXXV) was isolated in 82% yield. The reduction was highly stereospecific and none of the *threo* diastereomeric form could be detected (Looker and Thatcher, 1957).

$$\phi\underset{\underset{O}{\|}}{C}CN_2COOCH_3 \longrightarrow \phi-\underset{\underset{OH}{|}}{C}H-\underset{\underset{NH_2}{|}}{C}H-COOCH_3$$

(CLXXXIV)   (CLXXXV)
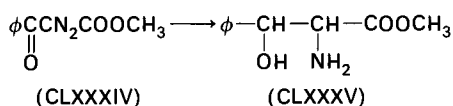
Similarly, hydrogenation of CLXXXVI in alcohol containing 0.9 mole of hydrogen chloride over 11% palladium chloride-on-carbon afforded CLXXXVII. If the reduction were carried out in neutral solution (hexane), condensation occurred and ethyl 2,5-dipentadecylhydro-3,5-pyrazinedicarboxylate was formed (Sallay *et al.*, 1954). Palladium would be expected to reduce the aromatic ketone in CLXXXIV but not the aliphatic ketone (CLXXXVI).

$$nC_{14}H_{29}CHBrCOCN_2CO_2C_2H_5 \xrightarrow[\substack{EtOH \\ Pd/C}]{HCl} nC_{14}H_{29}CH_2CO\underset{\underset{NH_3^+Cl^-}{|}}{C}HCO_2C_2H_5$$
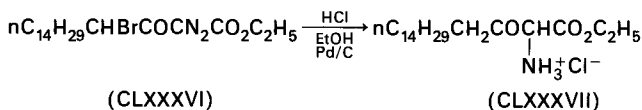
(CLXXXVI)   (CLXXXVII)

C. Nitroguanidines

Nitroguanidines undergo hydrogenolysis to the guanidine (Hafner and Evans, 1957). Hydrogenation of 2.5 gm CLXXXVIII over 0.125 gm palladium black in 62 ml 15% acetic acid afforded CLXXXIX (Milani *et al.*, 1955). A similar conversion of a complex nitroguanidine to a guanidine was carried out over 10% palladium-on-carbon in aqueous methanol (Stammer, 1961). (Other examples are given on page 173.)

$$F_3CCH_2NH\underset{\underset{NH_2}{|}}{C}=NNO_2 \longrightarrow F_3CCH_2NH\underset{\underset{NH}{\|}}{C}-NH_2$$

(CLXXXVIII)   (CLXXXIX)
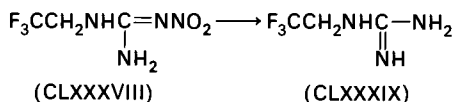
D. Azides

Hydrogenolysis of azides provides a convenient way of introducing an amino nitrogen (Bertele *et al.*, 1964; Krbechek and Takimoto, 1964). The

reduction proceeds without pressure drop, and for this reason most investigators seem to carry out the reaction longer than is probably necessary. Hydrogenation of 16.3 gm 2-azido-2-phenylethanol for 24 hours in 50 ml ethanol over 0.1 gm platinum oxide afforded β-amino-β-phenylethanol in 81% yield (McEwen *et al.*, 1952). Azide displaces halogen with inversion, and the hydrogenation provides an amine of inverted configuration. Remers *et al.* (1965) converted a complex *cis*-bromohydrin to the *trans*-aminohydrin by treatment of the bromohydrin with sodium azide, followed by hydrogenation over platinum oxide.

Attack of azide on epoxides also proceeds with inversion, and *trans*-2-aminocyclopentanol and *trans*-2-aminocyclohexanol were obtained by treatment of the appropriate epoxide with sodium azide, followed by hydrogenolysis over platinum oxide. Reductions carried out with benzoyl derivatives are accompanied by migration of the benzoyl function. Hydrogenation of *trans*-2-azidocyclohexyl benzoate afforded *trans*-2-benzamidocyclohexanol (VanderWerf *et al.*, 1954).
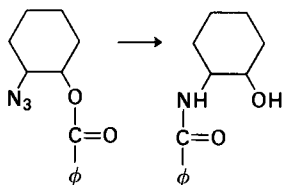
Hydrogenolysis of an azide proved useful in a synthesis of 2-amino-3-trifluoromethylbutyric acid (CXCII). Direct ammonolysis of the bromo ester (CXC) gave the 3-amino isomer instead of CXCII through initial loss of hydrogen bromide followed by addition of ammonia to the β-position of the crotonate. Treatment of CXC with excess sodium azide afforded ethyl 2-azido-3-trifluoromethylbutyrate (CXCI); 5 gm CXCI in 10 ml ethanol hydrogenated for 22 hours at 60 psig over 5% palladium-on-carbon afforded, after hydrolysis, CXCII in 56.5% yield (Loncrini and Walborsky, 1964).

$$CF_3CH(CH_3)CHBrCOOC_2H_5 \longrightarrow CF_3CH(CH_3)CH(N_3)COOC_2H_5$$
$$(CXCI) \quad \Big\downarrow \quad Pd/C$$
$$(CXC) \qquad\qquad CF_3CH(CH_3)CH(NH_2)COOH$$
$$(CXCII)$$
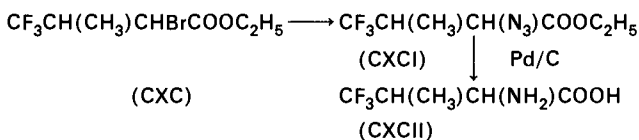
A convenient synthesis of 8-aminoadenosine involved hydrogenation of an azide function. Attempts to introduce an amino group into 8-bromoadenosine (CXCIII) by treatment with ammonia or with hydrazine failed, but treatment of CXCIII with sodium azide in dimethyl sulfoxide afforded 8-azidoadenosine, which could be reduced to 8-aminoadenosine. A mixture of 2.9 gm 8-azidoadenosine and 2 gm 5% palladium-on-carbon in 350 ml hot water was hydrogenated at 50 psig for 3.5 hours. 8-Aminoadenosine

(CXCIV) was obtained in 82% yield after recrystallization from water (Holmes and Robins, 1965).
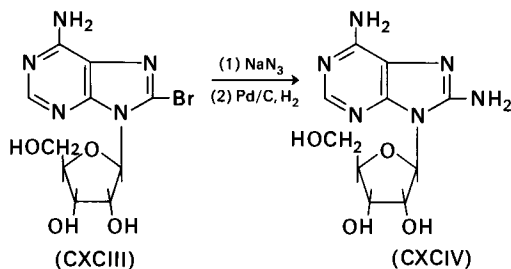
REFERENCES

Adams, R., and Gianturco, M., *J. Am. Chem. Soc.* **78**, 1922 (1956).
Adegoke, E. A., Ojechi, P., and Taylor, D. A. H., *J. Chem. Soc.* p. 415 (1965).
Agnello, E. J., Pinson, R., Jr., and Laubach, G. D., *J. Am. Soc.* **78**, 4756 (1956).
Aizikovich, M. A., and Petrov, A. A., *Zh. Obshch. Khim.* **28**, 3051 (1958).
Aizikovich, M. A., Maretina, I. A., and Petrov, A. A., *Zh. Obshch. Khim.* **28**, 3046 (1958).
Andersen, H. C., and Romeo, P. L., Sr., U.S. Patent 3,146,243, Aug. 25, 1964.
Andrews, L. H., and Lowy, A., *J. Am. Chem. Soc.* **56**, 1411 (1934).
Astill, B. D., and Boekelheide, V., *J. Am. Chem. Soc.* **77**, 4079 (1955).
Atherton, F. R., Openshaw, H. T., and Todd, A. R., *J. Chem. Soc.* p. 382 (1945a).
Atherton, F. R., Openshaw, H. T., and Todd, A. R., *J. Chem. Soc.* p. 660 (1945b).
Atherton, F. R., Howard, H. T., and Todd, A. R., *J. Chem. Soc.* p. 1106 (1948).
Baer, E., and Kates, M., *J. Am. Chem. Soc.* **72**, 942 (1950).
Baer, E., and Maurukas, J., *J. Am. Chem. Soc.* **74**, 158 (1952).
Baer, E., Maurukas, J., and Russell, M., *J. Am. Chem. Soc.* **74**, 152 (1952).
Bailey, P. S., *Chem. Rev.* **58**, 925 (1958).
Bailey, P. S., and Lutz, R. E., *J. Am. Chem. Soc.* **67**, 2232 (1945).
Baird, R., and Winstein, S., *J. Am. Chem. Soc.* **79**, 4238 (1957).
Baker, R. H., and Schlesinger, A. H., *J. Am. Chem. Soc.* **68**, 2009 (1946).
Baker, R. H., Cornell, K. H., and Cron, M. J., *J. Am. Chem. Soc.* **70**, 1490 (1948).
Ballou, C. E., and Fischer, H. O. L., *J. Am. Chem. Soc.* **76**, 3188 (1954).
Ballou, C. E., and Fischer, H. O. L., *J. Am. Chem. Soc.* **77**, 3329 (1955).
Ballou, C. E., and Fischer, H. O. L., *J. Am. Chem. Soc.* **78**, 1659 (1956).
Baltzly, R., and Buck, J. S., *J. Am. Chem. Soc.* **65**, 1984 (1943).
Baltzly, R., and Russell, P. B., *J. Am. Chem. Soc.* **72**, 3410 (1950).
Baltzly, R., and Russell, P. B., *J. Am. Chem. Soc.* **75**, 5598 (1953).
Baltzly, R., and Russell, P. B., *J. Am. Chem. Soc.* **76**, 5776 (1954).
Bartlett, M. F., Korzun, B., Sklar, R., Smith, A. F., and Taylor, W. I., *J. Org. Chem.* **28**, 1445 (1963).
Bergmann, M., and Zervas, L., *Chem. Ber.* **65B**, 1192, 1201 (1932).
Beringer, F. M., Galton, S. A., and Huang, S. J., *Tetrahedron* **19**, 809 (1963).
Berse, C., Boucher, R., and Piché, L., *J. Org. Chem.* **22**, 805 (1957).

Berson, J. A., and Suzuki, S., *J. Am. Chem. Soc.* **80**, 4341 (1958).

Bertele, E., Boos, H., Dunitz, J. D., Elsinger, F., Eschenmoser, A., Felner, I., Gribi, H. P., Gschwend, H., Meyer, E. F., Pesaro, M., and Scheffold, R., *Angew. Chem. Intern. Ed. English* **3**, 490 (1964).

Birkofer, L., *Chem. Ber.* **75B**, 429 (1942).

Birkofer, L., *Chem. Ber.* **80**, 83 (1947).

Birkofer, L., Bierwirth, E., and Ritter, A., *Chem. Ber.* **94**, 821 (1961).

Blomquist, A. T., and Jaffe, F., *J. Am. Chem. Soc.* **80**, 3405 (1958).

Blomquist, A. T., Stahl, R. E., Meinwald, Y. C., and Smith, B. H., *J. Org. Chem.* **26**, 1687 (1961).

Bodendorf, K., and Binder, B., *Arch. Pharm.* **287**, 326 (1954).

Bodendorf, K., and Wössner, W., *Ann. Chem.* **623**, 109 (1959).

Boekelheide, V., and Chang, M. Y., *J. Org. Chem.* **29**, 1303 (1964).

Bonner, W. A., and Zderic, A. A., *J. Am. Chem. Soc.* **78**, 3218 (1956).

Bonner, W. A., Zderic, A. A., and Casaletto, G. A., *J. Am. Chem. Soc.* **74**, 5086 (1952).

Bonner, W. A., Burke, N. I., Fleck, W. E., Hill, R. K., Joule, J. A., Sjöberg, B., and Zalkow, J. H., *Tetrahedron* **20**, 1419 (1964).

Bottini, A. T., Dev, V., and Stewart, M., *J. Org. Chem.* **28**, 156 (1963).

Bowman, R. E., Closier, M. D., and Islip, P. J., *J. Chem. Soc.* p. 470 (1965).

Breslow, R., Eicher, T., Krebs, A., Peterson, R. A., and Posner, J., *J. Am. Chem. Soc.* **87**, 1320 (1965).

Brewster, J. H., and Braden, W. E., Jr., *Chem. Ind. (London)* p. 1759 (1964).

Brown, E. V., *J. Am. Chem. Soc.* **79**, 3565 (1957).

Buck, J. S., and Baltzly, R., *J. Am. Chem. Soc.* **63**, 1964 (1941).

Burckhalter, J. H., Seiwald, R. J., and Scarborough, H. C., *J. Am. Chem. Soc.* **82**, 991 (1960).

Burn, D., Cooley, G., Davies, M. T., Hiscock, A. K., Kirk, D. N., Petrow, V., and Williamson, D. M., *Tetrahedron* **21**, 569 (1965).

Caldwell, A. G., and Jones, E. R. H., *J. Chem. Soc.* p. 599 (1946).

Callow, R. K., and Thompson, G. A., *J. Chem. Soc.* p. 3106 (1964).

Campbell, K. N., Sommers, A. H., and Campbell, B. K., *J. Am. Chem. Soc.* **68**, 140 (1946).

Carson, J. F., *J. Am. Chem. Soc.* **73**, 1850 (1951).

Carter, F. L., and Frampton, V. L., *Chem. Rev.* **64**, 497 (1964).

Cava, M. P., and Pohlke, R., *J. Org. Chem.* **28**, 1012 (1963).

Channing, D. M., Turner, P. B., and Young, G. T., *Nature* **167**, 487 (1951).

Ciganek, E., *J. Am. Chem. Soc.* **87**, 652 (1965).

Cline, R. E., Fink, R. M., and Fink, K., *J. Am. Chem. Soc.* **81**, 2521 (1959).

Closs, G. L., and Closs, L. E., *J. Am. Chem. Soc.* **85**, 99 (1963).

Cocker, W., Shannon, P. V. R., and Staniland, P. A., *J. Chem. Soc. (C)* p. 41 (1966).

Conrad, W. E., and Dec, S. M., *J. Org. Chem.* **23**, 1700 (1958).

Cookson, R. C., Hamon, D. P. G., and Parker, R. E., *J. Chem. Soc.* p. 5014 (1962).

Cope, A. C., and Ciganek, E., *In* "Organic Syntheses," Collected Vol. 4, p. 612. Wiley, New York, 1963. Ed. Rabjohn, N.

Cope, A. C., and LeBel, N. A., *J. Am. Chem. Soc.* **82**, 4656 (1960).

Cope, A. C., Liss, T. A., and Wood, G. W., *J. Am. Chem. Soc.* **79**, 6287 (1957).

Cram, D. J., and Bradshaw, J. S., *J. Am. Chem. Soc.* **85**, 1108 (1963).

Cram, D. J., and Hatch, M. J., *J. Am. Chem. Soc.* **75**, 33 (1953).

Cromwell, N. H., and Bambury, R. E., *J. Org. Chem.* **26**, 997 (1961).

Cross, A. D., U.S. Patent 3,139,426, June 30, 1964.

Dahn, H., Solms, V., and Zoller, P., *Helv. Chim. Acta* **35**, 2117 (1952).

Dart, M. C., and Henbest, H. B., *J. Chem. Soc.* p. 3563 (1960).

Dauben, W. G., and Hance, P. D., *J. Am. Chem. Soc.* **77**, 2451 (1955).

Dauben, W. G., Hayes, W. K., Schwarz, J. S. P. and McFarland, J. W., *J. Am. Chem. Soc.* **82**, 2232 (1960a).

Dauben, W. G., Schwarz, J. S. P., Hayes, W. H., and Hance, P. D., *J. Am. Chem. Soc.* **82**, 2239 (1960b).

Daves, G. D., Jr., Robins, R. K., and Cheng, C. C., *J. Am. Chem. Soc.* **84**, 1724 (1962).

Denton, D. A., McQuillin, F. J., and Simpson, P. L., *Proc. Chem. Soc.* p. 297 (1964).

deRopp, R. S., VanMeter, J. C., DeRenzo, E. C., McKerns, K. W., Pidacks, C., Bell, P. H., Ullman, E. F., Safir, S. R., Fanshawe, W. J., and Davis, S. B., *J. Am. Chem. Soc.* **80**, 1004 (1958).

Dickinson, J. P., Harley-Mason, J., and New, J. H., *J. Chem. Soc.* p. 1858 (1964).

Dornow, A., Hahmann, O., and Oberkobusch, R., *Ann. Chem.* **588**, 62 (1954).

Dürckheimer, W., and Cohen, L. A., *Biochemistry* **3**, 1948 (1964).

Emde, H., *Arch. Pharm.* **247**, 314, 351, 369 (1909).

Emde, H., *Helv. Chim. Acta* **15**, 1330 (1932).

Emde, H., and Kull, H., *Congr. Intern. Quim. Pura Apl., 9th, Madrid, 1934* **4**, 290 (1935).

Emde, H., and Kull, H., *Arch. Pharm.* **274**, 173 (1936).

Entel, J., Ruof, C. H., and Howard, H. C., *J. Am. Chem. Soc.* **73**, 4152 (1951).

Fajkos, J., *Chem. Listy* **52**, 1320 (1958).

Fields, D. L., Miller, J. B., and Reynolds, D. D., *J. Org. Chem.* **29**, 2640 (1964).

Fields, T. L., Kende, A. S., and Boothe, J. H., *J. Am. Chem. Soc.* **83**, 4612 (1961).

Filler, R., Piasek, E. J., and Mark, L. H., *J. Org. Chem.* **26**, 2659 (1961).

Fore, S. P., and Bickford, W. G., *J. Org. Chem.* **24**, 620 (1959).

Fore, S. P., and Bickford, W. G., *J. Org. Chem.* **26**, 2104 (1961).

Frankel, M., Zvilichovsky, G., and Knobler, Y., *J. Chem. Soc.* p. 3931 (1964).

Friedman, O. M., and Seligman, A. M., *J. Am. Chem. Soc.* **76**, 655 (1954).

Friedman, O. M., Klass, D. L., and Seligman, A. M., *J. Am. Chem. Soc.* **76**, 916 (1954).

Fuchs, J. J., U.S. Patent 3,068,275, Jan. 18, 1960.

Fuson, R. C., and Jackson, H. L., *J. Am. Chem. Soc.* **72**, 1637 (1950).

Galantay, E., Szabo, A., and Fried, J., *J. Org. Chem.* **28**, 98 (1963).

Garbisch, E. W., Jr., *J. Org. Chem.* **27**, 3363 (1962).

Gawron, O., Fondy, T. P., and Parker, D. J., *J. Org. Chem.* **28**, 700 (1963).

Gittos, M. W., *Chem. Ind. (London)* p. 1792 (1965).

Godfrey, J. C., Tarbell, D. S., and Boekelheide, V., *J. Am. Chem. Soc.* **77**, 3342 (1955).

Goering, H. L., Greiner, R. W., and Sloan, M. F., *J. Am. Chem. Soc.* **83**, 1391 (1961).

Green, M., and Solodar, W. E., U.S. Patent 3,187,049, June 1, 1965.

Griesbaum, K., Oswald, A. A., and Naegele, W., *J. Org. Chem.* **29**, 1887 (1964).

Griffin, B. S., and Burger, A., *J. Am. Chem. Soc.* **78**, 2336 (1956).

Gutsche, C. D., Bailey, D. M., Armbruster, C. W., Wendt, M. W., Kurz, J. L., Strohmayer, H. H., and Seligman, K. L., *J. Am. Chem. Soc.* **83**, 1404 (1961).

Hafner, L. S., and Evans, R., *J. Am. Chem. Soc.* **79**, 3783 (1957).

Haller, H. L., and Schaffer, P. S., *J. Am. Chem. Soc.* **55**, 3494 (1933).

Harnik, M., U.S. Patent 3,107,256, Oct. 15, 1963.

Hartung, W. H., *J. Am. Chem. Soc.* **50**, 3370 (1928).

Hartung, W. H., and Simonoff, R., *Org. Reactions* **7**, 263 (1953).

Hartzler, H. D., *J. Am. Chem. Soc.* **83**, 4990 (1961).

Hasek, R. H., Gott, P. G., and Martin, J. C., *J. Org. Chem.* **29**, 2510 (1964).

Heilbron, I. M., and Thompson, A., *J. Chem. Soc.* p. 883 (1929).

Herz, W., *J. Am. Chem. Soc.* **74**, 2928 (1952).

Hey, D. H., Leonard, J. A., and Rees, C. W., *J. Chem. Soc.* p. 5251 (1963).

Heyns, K., and Paulsen, H., *In* "Newer Methods of Preparative Organic Chemistry" (W. Foerst, ed.), Vol. 2, pp. 303–335. Academic Press, New York, 1963.

Hiskey, R. G., and Northrop, R. C., *J. Am. Chem. Soc.* **83**, 4798 (1961).

Hofmann, K., Lindenmann, A., Magee, M. Z., and Khan, N. H., *J. Am. Chem. Soc.* **74**, 470 (1952).

Holmes, R. E., and Robins, R. K., *J. Am. Chem. Soc.* **87**, 1772 (1965).

Holmquist, H. E., Marsh, F. D., Sauer, J. C., and Engelhardt, V. A., *J. Am. Chem. Soc.* **81**, 3681 (1959).

Horner, L., and Jürgens, E., *Chem. Ber.* **90**, 2184 (1957).

House, H. O., Wickham, P. P., and Müller, H. C., *J. Am. Chem. Soc.* **84**, 3139 (1962).

Howard, W. L., and Brown, J. H., Jr., *J. Org. Chem.* **26**, 1026 (1961).

Howton, D. R., and Kaiser, R. W., Jr., *J. Org. Chem.* **29**, 2420 (1964).

Hurd, C. D., and Jenkins, H., *J. Org. Chem.* **31**, 2045 (1966).

Inhoffen, H. H., Stoeck, G., Kölling, G., and Stoeck, U., *Ann. Chem.* **568**, 52 (1950).

Jacobson, H. I., Griffin, M. J., Preis, S., and Jensen, E. V., *J. Am. Chem. Soc.* **79**, 2608 (1957).

Jenny, E. F., and Druey, J., *J. Am. Chem. Soc.* **82**, 3111 (1960).

Jensen, F. R., and Coleman, W. E., *J. Am. Chem. Soc.* **80**, 6149 (1958).

Karabinos, J. V., and Serijan, K. T., *J. Am. Chem. Soc.* **67**, 1856 (1945).

Katritsky, A. R., and Monro, A. M., *J. Chem. Soc.* p. 1263 (1958).

Kaye, I. A., and Kogon, I. C., *J. Am. Chem. Soc.* **73**, 4893 (1951).

Kazanskii, B. A., Lukina, M. Yu., and Safonova, I. L., *Izv. Akad. Nauk SSSR Otd. Khim. Nauk* p. 102 (1958).

Kazanskii, B. A., Lukina, M. Yu., and Safonova, I. L., *Dokl. Akad. Nauk SSSR* **130**, 322 (1960).

Kharasch, M. S., and Priestly, H. M., *J. Am. Chem. Soc.* **61**, 3425 (1939).

Kilgour, G. L., and Ballou, C. E., *J. Am. Chem. Soc.* **80**, 3956 (1958).

Kindler, K., and Schrader, K., *Ann. Chem.* **564**, 49 (1949).

Kindler, K., and Schrader, K., *Arch. Pharm.* **283**, 190 (1950).

Kindler, K., Schärfe, E., and Henrich, P., *Ann. Chem.* **565**, 51 (1949).

King, H., and Work, T. S., *J. Chem. Soc.* p. 1307 (1940).

Knox, L. H., Villotti, R., Kincl, F. A., and Ringold, H. J., *J. Org. Chem.* **26**, 501 (1961).

Kochetkov, N. K., *Izv. Akad. Nauk SSSR Otd. Khim. Nauk* p. 47 (1954).

Kochetkov, N. K., and Sokolov, S. D., *Advan. Heterocyclic Chem.* **1**, 412 (1963).

Kochetkov, N. K., Khomatov, R. M., Budowsky, E. I., Karpeysky, M. Ja., and Severin, E. S., *Zh. Obshch. Khim.* **29**, 4069 (1959).

Kohler, E. P., and Davis, A. R., *J. Am. Chem. Soc.* **52**, 4520 (1930).

Krbechek, L., and Takimoto, H., *J. Org. Chem.* **29**, 1150 (1964).

Kuhn, R., and Haas, H. J., *Ann. Chem.* **611**, 57 (1958).

Lampe, W., and Smolinska, J., *Bull. Acad. Polon. Sci., Ser. Sci. Chim., Geol. et Geograph.* **6**, 481 (1958) (in English).

Laubach, G. D., U.S. Patent 2,794,033, May 28, 1957.

Lauer, W. M., and Dyer, W. S., *J. Am. Chem. Soc.* **64**, 1453 (1942).

Lawson, W. B., Patchornik, A., and Witkop, B., *J. Am. Chem. Soc.* **82**, 5918 (1960).

Lemal, D. M., and Shim, K. S., *J. Am. Chem. Soc.* **86**, 1550 (1964).

Leonard, N. J., and Foster, R. L., *J. Am. Chem. Soc.* **74**, 3671 (1952).

Leonard, N. J., and Jann, K., *J. Am. Chem. Soc.* **84**, 4806 (1962).

Leonard, N. J., Jann, K., Paukstelis, J. V., and Steinhardt, C. K., *J. Org. Chem.* **28**, 1499 (1963).

Lies, T., Plapinger, R. E., and Wagner-Jauregg, T., *J. Am. Chem. Soc.* **75**, 5755 (1953).

Loncrini, D. F., and Walborsky, H. M., *J. Med. Chem.* **7**, 369 (1964).

Looker, J. H., and Thatcher, D. N., *J. Org. Chem.* **22**, 1233 (1957).

Lott, W. A., and Shaw, E., *J. Am. Chem. Soc.* **71**, 70 (1949).

Lutz, R. E., and Wood, J. L., *J. Am. Chem. Soc.* **60**, 229 (1938).

Lythgoe, B., and Trippett, S., *J. Chem. Soc.* p. 471 (1959).

McAlees, A. J., and McCrindle, R., *Chem. Ind. (London)* p. 1869 (1965).
McCormick, J. R. D., and Jensen, E. R., U.S. Patent 3,019,260, Jan. 30, 1962.
McCormick, J. R. D., Jensen, E. R., Miller, P. A., and Doerschuk, A. P., *J. Am. Chem. Soc.* **82**, 3381 (1960).
McEwen, W. E., Conrad, W. E., and VanderWerf, C. A., *J. Am. Chem. Soc.* **74**, 1168 (1952).
McKay, A. F., Billy, J.-M., and Tarlton, E. J., *J. Org. Chem.* **29**, 291 (1964).
McKennis, H., Jr., and Yard, A. S., *J. Org. Chem.* **23**, 980 (1958).
McQuillin, F. J., and Ord, W. O., *J. Chem. Soc.* p. 3169 (1959).
McQuillin, F. J., and Simpson, P. L., *J. Chem. Soc.* p. 4726 (1963).
Magerlein, B. J., and Kagan, F., *J. Am. Chem. Soc.* **82**, 593 (1960).
Maley, F., Maley, G. F., and Lardy, H. A., *J. Am. Chem. Soc.* **78**, 5303 (1956).
Mallory, F. B., and Varimbi, S. P., *J. Org. Chem.* **28**, 1656 (1963).
Martin, J. C., Barton, K. R., Gott, P. G., and Meen, R. H., *J. Org. Chem.* **31**, 943 (1966).
Mattocks, A. M., and Hartung, W. H., *J. Am. Chem. Soc.* **68**, 2108 (1946).
Meinwald, J., and Frauenglass, E., *J. Am. Chem. Soc.* **82**, 5253 (1960).
Meinwald, J., Seidel, M. C., and Cadoff, B. C., *J. Am. Chem. Soc.* **80**, 6303 (1958).
Meinwald, J., Labana, S. S., and Chadha, M. S., *J. Am. Chem. Soc.* **85**, 582 (1963).
Meschke, R. W., and Hartung, W. H., *J. Org. Chem.* **25**, 137 (1960).
Milani, V., Skolnik, S., and Evans, R., *J. Am. Chem. Soc.* **77**, 2903 (1955).
Mitsui, S., and Kudo, Y., *Chem. Ind. (London)* p. 381 (1965).
Mitsui, S., and Nagahisa, Y., *Chem. Ind. (London)* p. 1975 (1965).
Mitsui, S., and Saito, H., *Nippon Kagaku Zasshi* **82**, 390 (1961).
Mitsui, S., Kamaishi, T., Imaizumi, S., and Takamura, I., *Nippon Kagaku Zasshi*, **83** (10), 1115 (1962).
Mitsui, S., Senda, Y., and Konno, K., *Chem. Ind. (London)* p. 1354 (1963).
Mitsui, S., Imaizumi, S., Senda, Y., and Konno, K., *Chem. Ind. (London)* p. 233 (1964).
Moffet, R. B., Hanze, A. R., and Seay, P. H., *J. Med. Chem.* **7**, 178 (1964).
Moore, J. A., and Marascia, F. J., *J. Am. Chem. Soc.* **81**, 6049 (1959).
Morrow, D. F., Butler, M. E., and Huang, H. C. Y., *J. Org. Chem.* **30**, 579 (1965).
Murin, B., and Riedl, W., *Chem. Ber.* **92**, 2029 (1959).
Nakano, T., Yang, T. H., and Terao, S., *Tetrahedron* **19**, 609 (1963).
Nesmeyanov, A. N., Kochetkov, N. K., Rybinskaya, M. I., and Uglova, E. V., *Bull. Acad. Sci. USSR Div. Chem. Sci. SSR (English Transl.)* 579 (1955).
Newham, J., *Chem. Rev.* **63**, 123 (1963).
Newman, M. S., and VanderWerf, C. A., *J. Am. Chem. Soc.* **67**, 233 (1945).
Newman, M. S., and Wiseman, E. H., *J. Org. Chem.* **26**, 3208 (1961).
Newman, M. S., Underwood, G., and Renoll, M., *J. Am. Chem. Soc.* **71**, 3362 (1949).
Nishimura, S., Onoda, S., and Nakamura, A., *Bull. Chem. Soc. Japan* **33**, 1356 (1960).
Noland, W. E., Cooley, J. H., and McVeigh, P. A., *J. Am. Chem. Soc.* **81**, 1209 (1959).
Ochiai, E., Ishikawa, M., and Katada, M., *Yakugaku Zasshi* **63**, 307 (1943).
Olin, S. M., U.S. Patent 3,029,243, Apr. 10, 1962.
Orlando, C. M., Jr., and Weiss, K., *J. Org. Chem.* **27**, 4714 (1962).
Overberger, C. G., and Marks, B. S., *J. Am. Chem. Soc.* **77**, 4097 (1955).
Overberger, C. G., Palmer, L. C., Marks, B. S., and Byrd, N. R., *J. Am. Chem. Soc.* **77**, 4100 (1955).
Park, G. J., and Fuchs, R., *J. Org. Chem.* **22**, 93 (1957).
Pearlman, W. M., U.S. Patent 3,239,563, Mar. 8, 1966.
Peterson, P. E., and Casey, C., *J. Org. Chem.* **29**, 2325 (1964).
Pigman, W., *In* "The Carbohydrates" (W. Pigman, ed.), p. 174. Academic Press, New York, 1957.
Pigulevski, G. V., and Sokolova, A. E., *Zh. Prikl. Khim.* **36**, 455 (1963).

Poos, G. I., and Rosenau, J. D., *J. Org. Chem.* **28**, 665 (1963).

Prostenik, M., Majhofer-Orescanin, B., Ries-Lesic, B., and Stanacev, N. Z., *Tetrahedron* **21**, 651 (1965).

Pryde, E. H., Anders, D. E., Teeter, H. M., and Cowan, J. C., *J. Org. Chem.* **25**, 618 (1960).

Pryde, E. H., Anders, D. E., Teeter, H. M., and Cowan, J. C., *J. Org. Chem.* **27**, 3055 (1962).

Reithel, F. J., and Claycomb, C. K., *J. Am. Chem. Soc.* **71**, 3669 (1949).

Remers, W. A., Roth, R. H., and Weiss, M. J., *J. Org. Chem.* **30**, 2910 (1965).

Renshaw, R. R., and Conn, R. C., *J. Am. Chem. Soc.* **60**, 745 (1938).

Richtmyer, N. K., *J. Am. Chem. Soc.* **56**, 1633 (1934).

Ross, J. M., Tarbell, D. S., Lovett, W. E., and Cross, A. D., *J. Am. Chem. Soc.* **78**, 4675 (1956).

Rowland, R. L., Latimer, P. H., and Giles, J. A., *J. Am. Chem. Soc.* **78**, 4680 (1956).

Rubashko, Z. Ya., *Zh. Obshch. Khim.* **34**(2), 584 (1964).

Russell, G. A., and Mayo, F. R., U.S. Patent 2,794,055, May 28, 1957.

Rylander, P. N., and Himelstein, N., Unpublished observations, Engelhard Ind., 1964a.

Rylander, P. N., and Himelstein, N., *Engelhard Ind. Tech. Bull.* **5**, 43 (1964b).

Rylander, P. N. and Karpenko, I., Unpublished observations, Engelhard Ind., 1960.

Rylander, P. N., and Rakoncza, N., Unpublished observations, Engelhard Ind., 1962.

Rylander, P. N., and Starrick, S., *Engelhard Ind. Tech. Bull.*, **7**, 106 (1966).

Rylander, P. N., and Steele, D. R., *Engelhard Ind. Tech. Bull.* **6**, 41 (1965).

Sallay, I., Dutka, F., and Fodor, G., *Helv. Chim. Acta* **37**, 778 (1954).

Sarel, S., and Breuer, E., *J. Am. Chem. Soc.* **81**, 6522 (1959).

Sauer, J. C., Cramer, R. D., Engelhardt, V. A., Ford, T. A., Holmquist, H. E., and Howk, B. W., *J. Am. Chem. Soc.* **81**, 3677 (1959).

Schmitz, E., *Advan. Heterocyclic Chem.* **2**, 92 (1963).

Schmitz, E., and Ohme, R., *Chem. Ber.* **94**, 2166 (1961).

Schreyer, R. C., U.S. Patent 3,092,654, June 4, 1963.

Schweizer, E. E., and Parham, W. E., *J. Am. Chem. Soc.* **82**, 4085 (1960).

Seebach, D., *Angew. Chem. Intern. Ed. English* **4**, 121 (1965).

Senda, Y., and Mitsui, S., *Nippon Kagaku Zasshi* **83**, 847 (1962).

Shaw, E., *J. Am. Chem. Soc.* **71**, 67 (1949).

Shaw, G., *J. Chem. Soc.*, p. 720 (1950).

Shaw, G., *J. Chem. Soc.* p. 1017 (1951).

Sheehan, J. C., and Hess, G. P., *J. Am. Chem. Soc.* **77**, 1067 (1955).

Sheehan, J. C., and Laubach, G. D., *J. Am. Chem. Soc.* **73**, 4752 (1951).

Sheradsky, T., Knobler, Y., and Frankel, M., *J. Org. Chem.* **26**, 1482 (1961).

Shoppee, C. W., Agashe, B. D., and Summers, G. H. R., *J. Chem. Soc.* p. 3107 (1957).

Shuikin, N. I., and Bel'skii, I. F., *Zh. Obshch. Khim.* **29**, 875 (1959).

Shuikin, N. I., Petrov, A. D., Glukhovtsev, V. G., and Karakhanov, R. A., *Izv. Akad. Nauk SSSR Otd. Khim. Nauk* p. 521 (1963).

Skita, A., *Chem. Ber.* **45**, 3312 (1912).

Smith, C. R., Jr., Wilson, T. L., Melvin, E. H., and Wolff, I. A., *J. Am. Chem. Soc.* **82**, 1417 (1960).

Smyrniotis, P. Z., Miles, H. T., and Stadman, E. R., *J. Am. Chem. Soc.* **80**, 2541 (1958).

Solodar, W. E., and Green, M., *J. Org. Chem.* **27**, 1077 (1962).

Sowden, J. C., and Kuenne, D. J., *J. Am. Chem. Soc.* **74**, 686 (1952).

Stammer, C. H., *J. Org. Chem.* **26**, 2556 (1961).

Stavely, H. E., *J. Am. Chem. Soc.* **64**, 2723 (1942).

Stedman, R. J., Swered, K., and Hoover, J. R. E., *J. Med. Chem.* **7**, 117 (1964).

Stein, W., and Rutzen, H., German Patent 1,139,477, Nov. 15, 1962.

Stevens, C. L., and Chang, C. H., *J. Org. Chem.* **27**, 4392 (1962).

Stevens, C. L., and Gasser, R. J., *J. Am. Chem. Soc.* **79**, 6057 (1957).

Stevens, C. L., Munk, M. E., Chang, C. H., Taylor, K. G., and Schy, A. L., *J. Org. Chem.* **29**, 3146 (1964).

Stevens, T. E., and Freeman, J. P., *J. Org. Chem.* **29**, 2279 (1964).

Stumpf, W. S., *Z. Elektrochem.* **57**, 690 (1953).

Tarbell, D. S., Carman, R. M., Chapman, D. D., Cremer, S. E., Cross, A. D., Huffman, K. R., Kunstmann, M., McCorkindale, N. J., McNally, J. G., Jr., Rosowsky, A., Varino, F. H. L., and West, R. L., *J. Am. Chem. Soc.* **83**, 3096 (1961).

Taub, D., Kuo, C. H., Slates, H. L., and Wendler, N. J., *Tetrahedron* **19**, 1 (1963).

Taylor, E. C., and Driscoll, J. S., *J. Org. Chem.* **25**, 1716 (1960).

Taylor, E. C., and Garcia, E. E., *J. Org. Chem.* **29**, 2116 (1964).

Taylor, E. C., Barton, J. W., and Osdene, T. S., *J. Am. Chem. Soc.* **80**, 421 (1958).

Temnikova, T. I., and Kropachev, V. A., *Zh. Obshch. Khim.* **19**, 2069 (1949).

Tener, G. M., and Khorana, H. G., *J. Am. Chem. Soc.* **80**, 1999 (1958).

Thompson, Q. E., *J. Org. Chem.* **27**, 4498 (1962).

Tomita, M., and Tani, C., *Yakugaku Zasshi* **64**, 242 (1944).

Ukita, T., and Hayatsu, H., *J. Am. Chem. Soc.* **84**, 1879 (1962).

Ukita, T., Nagasawa, K., and Irie, M., *J. Am. Chem. Soc.* **80**, 1373 (1958).

Ullman, E. F., *J. Am. Chem. Soc.* **81**, 5386 (1959).

Ushakov, M. I., and Mikhailov, B. M., *Zh. Obshch. Khim.* **7**, 249 (1937).

VanderWerf, C. A., Heisler, R. Y., and McEwen, W. E., *J. Am. Chem. Soc.* **76**, 1231 (1954).

Vellturo, A. F., and Griffin, G. W., *J. Am. Chem. Soc.* **87**, 3021 (1965).

Verzele, M., Acke, M., and Anteunis, M., *J. Chem. Soc.* p. 5598 (1963).

von Wittenau, M. S., *J. Org. Chem.* **29**, 2746 (1964).

Wagner, A. F., Wittreich, P. E., Arison, B., Trenner, N. R., and Folkers, K., *J. Am. Chem. Soc.* **85**, 1178 (1963).

Walker, G. N., *J. Org. Chem.* **27**, 1929 (1962).

Wang, C.-H., and Cohen, S. G., *J. Org. Chem.* **26**, 3301 (1961).

Wenkert, E., Carney, R. W. J., and Kaneko, C., *J. Am. Chem. Soc.* **83**, 4440 (1961).

Westphal, O., and Stadler, R., *Angew. Chem. Intern. Ed. English* **2**, 327 (1963).

White, J., *J. Biol. Chem.* **106**, 141 (1934).

Whitmore, W. F., and Gebhart, A. I., *J. Am. Chem. Soc.* **64**, 912 (1942).

Wiberg, K. B., and Ciula, R. P., *J. Am. Chem. Soc.* **81**, 5261 (1959).

Wiberg, K. B., and Hutton, T. W., *J. Am. Chem. Soc.* **76**, 5367 (1954).

Witkop, B., and Foltz, C. M., *J. Am. Chem. Soc.* **79**, 197 (1957).

Witkop, B., and Patrick, J. B., *J. Am. Chem. Soc.* **73**, 2188 (1951).

Witkop, B., and Patrick, J. B., *J. Am. Chem. Soc.* **74**, 3855 (1952).

Wolfrom, M. L., Gibbons, R. A., and Huggard, A. J., *J. Am. Chem. Soc.* **79**, 5043 (1957).

Wright, W. B., Jr., Brabander, H. J., and Hardy, R. A., Jr., *J. Org. Chem.* **26**, 485 (1961).

Zajcew, M., *J. Am. Oil Chemists' Soc.* **35**, 475 (1958).

Zaugg, H. E., Freifelder, M., Glenn, H. J., Horrom, B. W., Stone, G. R., and Vernsten, M. R., *J. Am. Chem. Soc.* **78**, 2626 (1956).

Zderic, J. A., Rivera, M. E. C., and Limon, D. C., *J. Am. Chem. Soc.* **82**, 6373 (1960).

Zervas, L., *Naturwissenschaften* **27**, 317 (1939).

Zervas, L., and Dilaris, I., *J. Am. Chem. Soc.* **77**, 5354 (1955).

Zilkha, A., and Golik, U., *J. Org. Chem.* **28**, 2007 (1963).

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